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

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Clinical Study Protocol SYD985.002

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
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Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
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1 Protocol synopsis

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

Objectives:
The primary objective of this study is:

- To demonstrate that SYD985 is superior to physician's choice in prolonging progression-free survival (PFS) on the basis of the blinded independent central review of tumour assessment.

The secondary objectives of this study are to compare the two treatment groups with respect to:

- Overall survival (OS);
- Objective response rate (ORR) on the basis of the blinded independent central review;
- Investigator assessed PFS;
- Patient reported outcomes for health related quality of life;
- Safety and tolerability.

Study design:
This study is designed as a randomized, active-controlled, superiority study in patients with unresectable locally advanced or metastatic HER2-positive breast cancer. The patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment.

Eligible patients will be randomly assigned (2:1) to receive SYD985 or physician's choice treatment until disease progression, unacceptable toxicity or study termination by the Sponsor. During treatment, patients will have to visit the clinical site to assess efficacy, quality of life (QoL), and safety using standardized criteria.

Duration of patient treatment and participation:
After a screening period of maximally 28 days, patients who are eligible will be randomized and treated until disease progression or unacceptable toxicity. Upon treatment discontinuation patients should return for a treatment discontinuation visit 4-6 weeks after the last administration of study drug. Thereafter patients will be contacted to follow up on clinical disease progression, unresolved AEs, new anticancer therapies, and overall survival every 3 months after the treatment discontinuation visit up to death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first.

Study population:
When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per Summary of Product Characteristics/Prescribing Information for the physician's choice treatment options, should be taken into account. **Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.**

The study population will consist of patients with HER2-positive unresectable locally advanced or metastatic breast cancer complying with the following in- and exclusion criteria:

Inclusion criteria

1. Female patients, age ≥ 18 years old at the time of signing informed consent;
2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;
3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component, or patients who have bone-only metastases requiring endocrine therapy or patients with non-visceral metastases requiring endocrine therapy, are not eligible;
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
7. Estimated life expectancy > 12 weeks at randomization;
8. Adequate organ function, evidenced by the following (local) laboratory results:
   - Absolute neutrophil count ≥ 1.5 x 10^9/L;
   - Platelet count ≥ 100 x 10^9/L;
   - Hemoglobin ≥ 9.0 g/dL;
   - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN);
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases);
   - Serum creatinine ≤ 1.5 x ULN;
9. For women of childbearing potential, two methods of effective contraception must be used during the study and up to 6 months after last study treatment. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity.

Exclusion criteria

1. Having been treated with:
   a. SYD985 at any time;
   b. Anthracycline treatment within 12 weeks prior to randomization;
   c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to randomization;
   d. Radiotherapy within 2 weeks prior to randomization;
   e. Hormone therapy within 1 week prior to randomization;

   The patient must have sufficiently recovered from any treatment-related toxicities to NCI CTCAE Grade ≤1 (except for toxicities not considered a safety risk for the patient at the investigator's discretion);
2. History of infusion-related reactions and/or hypersensitivity to trastuzumab, (ado-)trastuzumab emtansine or excipients of the study drug which led to permanent discontinuation of the treatment;
3. History of keratitis;
4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. Left ventricular ejection fraction (LVEF) < 50% as assessed by either echocardiography or multigated acquisition (MUGA) scan at screening, or a history of clinically significant decrease in LVEF during

previous treatment with trastuzumab or (ado-)trastuzumab emtansine leading to permanent discontinuation of treatment;
6. Cardiac troponin value above the ULN (local laboratory) at screening;
7. History (within 6 months prior to randomization) of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to randomization. Patients with prior treatment of brain metastases must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;
9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
10. Known active Hepatitis B or C infection;
11. Major surgery within 4 weeks prior to randomization;
12. Pregnancy or lactation;
13. Other condition, which in the opinion of the investigator, would compromise the safety of the patient or the patient's ability to complete the study.

Study medication, mode of administration:

Investigational medicinal product:

SYD985 (trastuzumab vc-*seco*-DUBA, Byondis BV, The Netherlands)

Patients in the investigational group will be treated every three weeks (Q3W) with 1.2 mg/kg SYD985. SYD985 is an antibody-drug conjugate (ADC) comprised of Byondis' HER2-targeting monoclonal IgG1 antibody trastuzumab ([redacted]) covalently bound to a linker-drug (SYD980). The linker-drug contains a cleavable linker and the prodrug *seco*-duocarmycin-hydroxybenzamide-azaindole (*seco*-DUBA, [redacted]). The linker can be cleaved by proteases in the tumour at the dipeptide valine-citrulline (vc) motif, which releases the active DNA-alkylating toxin (DUBA, SYD986).

Drug product vials contain 80 mg sterile lyophilized SYD985 which should be reconstituted prior to use with 8.0 mL sterile water for injection to yield a solution of 10 mg/mL. SYD985 drug product vials should be stored at 2 to 8 °C (36-46 °F) until use.

The calculated amount of solution should be added to an infusion bag containing 0.9% sodium chloride without other additives. If reconstituted vials or the prepared infusion bag is not used immediately, it can be stored at 2 to 8 °C (36-46 °F) for a maximum of 24 hours up to start of infusion.

SYD985 is to be administered intravenously over 60 minutes for the first infusion, subsequent infusions can be given over 30 minutes.

Reference therapy: Treatment of physician's choice

Patients in the reference group will be treated with approved systemic therapy administered as per local practice and according to the needs of each patient. Investigators can choose between four pre-specified treatment regimens:

- Option 1: Lapatinib + Capecitabine
- Option 2: Trastuzumab + Capecitabine
- Option 3: Trastuzumab + Vinorelbine
- Option 4: Trastuzumab + Eribulin

Study assessments and procedures (see also flowchart):

The informed consent form (ICF) must be signed before any study-related procedure is performed. A specific "HER2 testing"-ICF may be used to allow the central assessment of HER2 tumour status on tumour tissue.

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

The HER2 tumour status will be assessed by a central laboratory using IHC and ISH on archived (or fresh) material to determine eligibility.

Blood samples will be drawn to assess pharmacokinetic parameters, anti-SYD985 antibodies, circulating tumour DNA (ctDNA), and serum HER2 extracellular domain (ECD) levels at a central laboratory. Blood samples for blood chemistry, haematology and cardiac biomarkers will be measured by the local and central laboratory. Urinalysis will be performed locally.

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 42 weeks and every 9 weeks thereafter. Tumour responses will be assessed by the investigator / radiologist and by a central image analysis centre using the RECIST criteria (version 1.1).

EORTC QLQ-C30 and breast module QLQ-BR23 questionnaires will be used on day 1 of the first 5 cycles and subsequently every 2nd cycle to monitor changes in the patient's QoL.

Patients will be contacted to follow up on clinical disease progression, unresolved AEs, new anticancer therapies, and overall survival every 3 months after the treatment discontinuation visit up to death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first.

Statistical methods:

Data sets:

The primary analysis set will include all patients who were randomized in the study (i.e. the Full Analysis Set (FAS)). For efficacy, patients will be analyzed according to the treatment group to which they were randomized. For safety, patients will be analyzed according to the actual treatment they received, regardless the randomization.

Efficacy analysis

Primary outcome:

The primary PFS analysis will be performed when at least 256 PFS events have occurred, or when at least 95% of patients have discontinued treatment, and only after all patients have been enrolled. The median time-to-event outcomes and corresponding 95% Confidence Intervals (CIs) for each treatment group will be estimated using Kaplan-Meier methods. The two-sided log-rank test, stratified by the protocol-defined randomization factors will be used to compare time-to-event outcomes between treatment groups. Hazards Ratios and corresponding 95% CIs will be estimated using Cox proportional hazards models, stratified by the protocol defined randomization factors. Superiority of SYD985 to physician's choice will be analyzed with the log-rank test at alpha 0.05.

Secondary outcomes:

- Overall survival (OS);
- Objective response rate (ORR) on the basis of the blinded independent central review;

- Investigator assessed PFS;
- Patient reported outcomes for health related quality of life.

Safety analysis

The safety profile will be assessed by evaluation of:

- Incidence and severity of AEs;
- Laboratory abnormalities;
- Specific safety assessments (LVEF, ECG, ophthalmological exams).

The evaluation will be performed using descriptive statistics.

Sample size:

In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 30% drop out in the physician's choice group and 40% in the SYD985 group, a minimal number of 423 patients is required. Allocation is 2:1 resulting in 282 to be allocated to the SYD985 group and 141 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (1 or 2/more than 2), and prior treatment with pertuzumab (yes/no) as stratification factors.

Data Monitoring Committee:

Safety will be monitored on an ongoing basis during the entire study by an independent external Data Monitoring Committee (DMC), of which the composition, roles and responsibilities will be described in a separate charter. As part of their evaluation the DMC assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates. Based on their pre-planned interim evaluation, the independent DMC has recommended to adjust the sample size and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis.

Number of study sites:

The number of participating sites will be approximately 100 to ensure timely enrolment of the required number of patients. Sites will be located in Europe, Singapore and North-America.

Planned clinical study period:

First patient first visit: Q3 2017
Last patient first visit: H1 2020
Last patient last visit: H1 2021

1.1 Study flowchart (assessments and procedures)

	Screening	Cycle 1				Cycle 2			Cycle 3	Cycle 4			Cycle 5 onwards	Treatment disc.	Survival Follow-up
Visit day	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 2**	**Day 15**	**Day 1**	**28-42 days after last dose of study treatment[20]**	**Every 3 months after last contact[18]**
Visit window (days)				**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 3**		**± 3**	**± 3**		**± 14**
Informed consent[1]	✓														
Demographics	✓														
Medical history	✓														
In/exclusion criteria	✓	✓													
Physical examination	✓	Examination only whenever indicated by AE review												✓	
Vital signs[21]	✓	✓[2]		✓	✓	✓[2]	✓	✓	✓[2]	✓[2]			✓[2]	✓	
Weight, Height (only at screening)	✓	✓[3]				✓[3]			✓[3]	✓[3]			✓[3]	✓	
ECOG performance status	✓	✓[2]				✓[2]			✓[2]	✓[2]			✓[2]	✓	
Central HER2 assessment[4]	✓														
Haematology / blood chemistry / Cardiac troponin[6]	✓	✓[5]		✓	✓	✓[5]	✓	✓	✓[5]	✓[5]			✓[5]	✓	
Urinalysis	✓	✓[5]				✓[5]			✓[5]	✓[5]			✓[5]	✓	
Pregnancy test[7]	✓	✓				✓			✓	✓			✓	✓	
Blood sample(s) - PK[8]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Blood sample - immunogenicity[9]		✓[2]				✓[2]			✓[2]	✓[2]			✓[2]	✓	
Blood sample - serum HER2 ECD		✓[2]				✓[2]			✓[2]	✓[2]			✓[2]	✓	
Blood sample - ctDNA		✓[2]												✓	
Ophthalmological examination[10]	✓					✓				✓ + every 2nd cycle				✓	

	Screening	Cycle 1				Cycle 2			Cycle 3	Cycle 4			Cycle 5 onwards	Treatment disc.	Survival Follow-up
Visit day	**Day -28 to -1**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 2**	**Day 15**	**Day 1**	**28-42 days after last dose of study treatment[20]**	**Every 3 months after last contact[18]**
Visit window (days)				**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 3**		**± 3**	**± 3**		**± 14**
LVEF[10, 11]	✓					✓				✓ + every 4th cycle				✓	
ECG[12]	✓	✓	✓[13]			✓			✓	✓ + every 4th cycle	✓[13]			✓	
Tumour evaluation[14,15]	✓	Every 6 weeks after randomization during the first 42 weeks and every 9 weeks thereafter												✓[17]	
CT or MRI of brain[15]	✓	Per clinical indication												Per clinical indication	
Whole body bone scan[15]	✓	Per clinical indication												Per clinical indication	
QoL questionnaires		✓				✓			✓	✓			✓ + every 2nd cycle	✓	
Study drug administration[16]		✓				✓			✓	✓			✓		
(S)AEs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Previous and concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[19]
Survival information (progression, death)														✓	✓

General note: in case assessments show abnormal results that warrant more extensive monitoring for safety, additional visits and assessments should be considered. For patients on physician's choice treatment in addition to the assessments in the flowchart guidance from the Summary of Product Characteristics/Prescribing Information of the specific treatments should be followed with regards to patient monitoring.

1 Following signing the "Study"-ICF an eligible patient should be randomized within 28 days. A "HER2 testing"-ICF may be used to assess the HER2 tumour status on archival tumour tissue to determine patient eligibility;

2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment (should be done on Day1 of the new cycle, but may be done up to 3 days before) and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;
16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.
20 The end of treatment visit needs to be performed 28-42 days after the last dose of study drug or before new anticancer treatment is initiated, whichever comes first.
21 Vital signs include blood pressure, heart rate, body temperature, and oxygen saturation by pulse oximetry.

PK blood sampling scheme for the SYD985 treatment group

Cycle	Day	Sampling time*
Cycle 1	1	Pre-dose
		End of infusion
	2	24 hours (± 2h) after end of infusion
	8	During the visit
	15	During the visit
Cycle 2	1	Pre-dose
		End of infusion
	8	During the visit
	15	During the visit
Cycle 3	1	Pre-dose
		End of infusion
Cycle 4	1	Pre-dose
		End of infusion
	2	24 hours (± 2h) after end of infusion
	15	During the visit
Cycle 5 onwards	1	Pre-dose
Treatment discontinuation		During the visit

* PK will be assessed for total SYD985 (includes SYD985 with a drug-to-antibody ratio (DAR) of ≥ 0), conjugated SYD985 (includes SYD985 with a DAR of ≥1), and for the free toxin (DUBA, SYD986) in cycle 1 to 4. From cycle 5 onwards PK will be assessed for total SYD985 only. One or two spare aliquots will be stored for re-analysis purposes, a DAR average assay (if considered relevant and feasible), and/or other exploratory PK, biotransformation/metabolite identification or mode of action related assays which may turn out to be useful for further development of duocarmycin-based ADCs. In case PK, immunogenicity, efficacy and/or safety data indicate a possible development of anti-SYD985 antibodies, the Sponsor may discuss an intensified PK and/or immunogenicity sampling scheme with the site on a case-by-case basis.

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: ***Clinical Project Leader*** Telephone Number: E-Mail: ***Biostatistician*** Telephone Number: E-Mail:	[redacted]
Scientific Steering Committee (Chair):	[redacted]
CRO (clinical services)	[redacted]
EDC, randomization and QoL services	[redacted]
IMP logistics: (for SYD985)	[redacted]

Central Image Analysis: **(RECIST evaluation)**	[redacted]
Central ECG Centre: **(ECG evaluation)**	[redacted]
Central Laboratory: **(Safety laboratory & logistics)**	[redacted]
Central Laboratory: **(for PK SYD986, total SYD985, SYD985 DAR≥1 and immunogenicity)**	[redacted]
Central Laboratory: **(for HER2 Tumour expression)**	[redacted]

3 Table of contents

4 List of abbreviations

ABGs	Arterial Blood Gases
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
BMI	Body Mass Index
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
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
DAR	Drug-to-antibody ratio
DMC	Data Monitoring Committee
ECD	Extracellular domain
ECG	Electro Cardio Gram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
ESMO-MCBS	European Society of Medical Oncology Magnitude of Clinical Benefit Scale
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
HDL	High Density Lipoprotein
HER2	Human Epidermal growth factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ICR	Independent central review

IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal product Dossier
IRB	Institutional review Board
ISF	Investigator Site File
ISH	In situ hybridization
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine system
IXRS	Interactive voice/web Response System
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean cell volume
MHRA	Medicines and Health Care products Regulatory Agency
MUGA	Multigated acquisition
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PFS	Progression-Free Survival
PFTs	Pulmonary Function Tests
PK	Pharmacokinetics
PP	Per-Protocol
PPS	Per-Protocol Set
PR	Partial response
Q3W	Dosing every three weeks
QoL	Quality of life
RBC	Red Blood cell Count
RECIST	Response Evaluation Criteria for Solid Tumours
SAE	Serious Adverse Event
SAF	Safety (population)
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC/PI	Summary of Product Characteristics/Prescribing Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	Byondis's monoclonal IgG1 antibody trastuzumab (which is similar to Herceptin®)
[redacted]	a cleavable linker and the prodrug *seco*-duocarmycin-hydroxybenzamide-azaindole (*seco*-DUBA)

SYD985	trastuzumab vc-*seco*-DUBA
SYD986	DUocarmycin hydroxyBenzamide Azaindole (DUBA, active toxin)
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
ILN	Upper limit of normal
vc	Valine-citrulline
WBC	White Blood cell Count

5 Introduction

5.1 Therapeutic background and study rationale

Advanced and metastatic breast cancer remains incurable, and an estimated 450,000 patients globally die from breast cancer per annum.[1] Of these, approximately 15-20% are patients with Human Epidermal growth factor Receptor 2 (HER2) positive disease. Amplification and over-expression of HER2 are associated with shortened survival.[2;3] The development of trastuzumab as a HER2-targeting agent represented a paradigm shift in breast cancer from non-specific chemotherapy to a molecular targeted approach. However, despite the efficacy of trastuzumab, most patients develop progressive disease during or after trastuzumab treatment, and additional intervention is required. In view of the evidence that HER2 over-expression persists and remains relevant beyond progression[2-4] strategies to overcome insensitivity to treatment have involved changing the HER2-directed agent or switching chemotherapies in subsequent lines of treatment.[5;6]

Four HER2-targeting therapies have been approved up to now in the EU and 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). With the exception of (ado-)trastuzumab emtansine these HER2-targeting treatments are used in combination therapy regimens in the locally advanced or metastatic setting. Sooner or later the disease progresses again and the patient will become refractory to that specific HER2-targeting therapy combination. For patients whose tumour progress on an anti-HER2 therapy (whether or not combined with cytotoxic or endocrine agent) it is important that additional anti-HER2 therapy is offered with subsequent treatment since it is beneficial to continuously keep on targeting the HER2 pathway.[6]
Currently recommended first-line treatment for HER2-positive advanced or metastatic breast cancer is trastuzumab, pertuzumab and a taxane. If the cancer progresses during or after first-line therapy (ado-)trastuzumab emtansine is recommended for 2nd-line treatment. Once a patient becomes refractory to these agents, either as a single agent or as combination therapy, different treatment options are being used. Often standard chemotherapy or hormonal therapy will be combined with an anti-HER2 agent. There is insufficient evidence to recommend a specific regimen and in general it is the choice of the physician what is prescribed.

Byondis developed a new HER2-targeting therapy, SYD985, which is comprised of Byondis's monoclonal IgG1 antibody trastuzumab ([redacted], similar to Herceptin®) covalently bound to a linker-drug (SYD980). The linker-drug contains a cleavable linker and the prodrug *seco*-DUocarmycin-hydroxyBenzamide-Azaindole (*seco*-DUBA, [redacted]).
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-citruline (vc) motif by proteases. Upon cleavage, two self-elimination reactions occur to generate the prodrug (*seco*-DUBA, [redacted]), which then spontaneously rearranges to form the active toxin (DUBA, [redacted]). The active toxin alkylates DNA resulting in DNA damage in both dividing and non-dividing cells, and ultimately cell death. SYD985 most likely also induces a bystander effect through extra-cellular cleavage of the linker-drug within the tumour by extracellular proteases. This bystander effect may not only kill the HER2-positive cell but potentially also (HER2-negative) neighbouring cells.
The intent of this Phase III study is to investigate the efficacy and safety of SYD985 for the treatment of patients with unresectable locally advanced or metastatic HER2-positive breast cancer who have had progression either during or after at least two HER2-targeting treatment regimens in the locally advanced or metastatic setting or after (ado-)trastuzumab emtansine treatment.

5.2 Patient population rationale

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

Part I of this Phase I study was a dose escalation study with patients with solid tumors of any origin. In this part 39 patients were enrolled and treated. For breast cancer patients only (n=25), the objective response rate (ORR) was 36.0% (95% CI 18.0; 57.5), with partial responses in 5 HER2-positive and 4 HER2-negative breast cancer patients. The Kaplan Meier estimate of the median (95% CI) duration of progression free survival (PFS) was 24.3 weeks (12.0, 36.4) for the breast cancer patients. All but one HER2-positive breast cancer patients were pretreated with trastuzumab and (ado-)trastuzumab emtansine (see Investigator's Brochure for details). Therefore, SYD985 represents a reasonable treatment option for the intended patient population in this study.

Part II of the Phase I study is ongoing; expanded patient cohorts with specific cancer types, including 50 heavily pre-treated patients with late-line HER2-positive locally advanced or metastatic breast cancer, are being evaluated for safety and efficacy.

5.3 Dosage rationale

SYD985 will be administered in a dose of 1.2 mg/kg once every three weeks. After evaluation of all available data of the dose-escalation part of the Phase I study, it was concluded that doses above 1.2 mg/kg did not seem to improve the benefit-risk as compared to the 1.2 mg/kg dose. Therefore, it was decided to select 1.2 mg/kg as the recommended Phase II dose (see Investigator's Brochure for details).

The 3-weekly interval was investigated in the dose-escalation part of the Phase I study and in addition, this interval is most convenient if SYD985 may be combined, in future studies, with other therapies which have predominantly 3-weekly intervals as well. Dosing delays and reductions are allowed to reduce toxicity in an individual patient (Section 9.5).

5.4 Primary endpoint rationale

The primary endpoint of this study is to demonstrate that SYD985 is superior to physician's choice in prolonging PFS on the basis of the blinded independent central review of tumour assessment.

In a recent study with HER2-positive locally advanced or metastatic breast cancer patients, the TH3RESA study, the median (95% CI) PFS in the physician's choice group was 3.3 (2.89 - 4.14) months. Since this study was conducted new treatments have been approved and are being prescribed to these patients in first and second line treatment. Therefore, it can be expected that patients included in the current study will have a prognosis that is at best comparable, but likely worse, than the prognosis for patients in the physician's choice group in the TH3RESA study. The aim of this study is to show an improvement of at least 35% in PFS by SYD985, as compared to physician's choice, in addition this is expected to be associated with a gain of at least 1.5 months in PFS. The European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)[7] indicates that

this represents a direct clinical benefit to the patient if using standard treatment the median PFS is ≤ 6 months.

5.5 Safety considerations

5.5.1 SYD985 treatment

This section is primarily based on the data from the ongoing Phase I study. Additionally, non-clinical studies and data from trastuzumab and (ado-)trastuzumab emtansine have been taken into account. Please refer to the SYD985 Investigator's Brochure for further information. It should be taken into account that clinical safety data and treatment duration with SYD985 is limited and that toxicity other than described in the Investigator's Brochure may evolve. For the most up to date information one should always refer to the current version of the Investigator's Brochure.

The most common drug-related AEs reported in the ongoing Phase I study are:

- Conjunctivitis, lacrimation increased, dry eye, keratitis, and blepharitis;
- Fatigue and pyrexia;
- Nausea, stomatitis, vomiting, constipation;
- Dry skin, alopecia, skin hyperpigmentation;
- Neutropenia, anemia, thrombocytopenia;
- Dysgeusia, headache;
- Decreased appetite;
- Infusion related reactions.

Adverse event with important safety consideration are described in more detail below.

Interstitial Lung Disease ILD/Pneumonitis

ILD/Pneumonitis was reported in the Phase I study. ILD/Pneumonitis and lung consolidations are also reported for other anticancer drugs, including anti-PD1 antibodies[8;9], everolimus (mTOR inhibitor), and the anti-HER2 agents lapatinib and (ado-)trastuzumab emtansine[10].

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 IDL/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug-induced ILD/pneumonitis. ILD/pneumonitis evaluation (regardless of stage) should always include a pulmonary consult, a high resolution CT, pulmonary function testing (PFTs), pulse oximetry and arterial blood gases (ABGs).

To detect pulmonary toxicity in an early stage, the tumour evaluation CT scans, which are initially done every 6 weeks, should be carefully evaluated for lung changes e.g. by means of high resolution CT. Patients should be advised to promptly report any new or worsening respiratory symptoms.

Eye toxicity

Eye toxicity was commonly reported in the Phase I study, in more than 50% of the patients. Drug-related eye disorders included e.g. lacrimation increased (watery eyes), dry eyes, conjunctivitis, keratitis, periorbital oedema, and blepharitis. The most common severe eye toxicity (grade 3) was keratitis.

Ophthalmological examination is required every other cycle to closely monitor eye toxicity. It is recommended to treat any eye disorder in an early stage, if possible. Prophylactic lubricating eye drops will be prescribed for all patients in the SYD985 group, to be used 3 times a day or as needed. Patients are advised not to wear contact lenses or rub their eyes during SYD985 treatment. Further evaluation of prophylactic measures is ongoing in the Phase I study and will be implemented per protocol amendment if shown to be effective.

Cardiac toxicity

Cardiac safety should be monitored in oncology patients commonly pre-treated with anthracycline therapy and/or treated with HER2-targeting agents. Transient, LVEF decreases have been observed in the Phase I study. LVEF decreases have also been observed in patients treated with trastuzumab and (ado-)trastuzumab emtansine and these often occur in the early treatment cycles[11-13]. Patients treated with these drugs are at increased risk of developing congestive heart failure or dysfunction, particularly following anthracycline therapy.
Cardiotoxicity is closely monitored in the study by performing LVEF and ECGs, and by measuring cardiac troponin regularly during SYD985 treatment. Patients with an increased risk of developing cardiac dysfunction, as defined in this protocol, are not eligible to participate in the study. Any clinically relevant electrolyte disturbance (e.g. hypomagnesaemia and hypokalemia) should be corrected as appropriate.

Infusion related reactions

Infusion related reactions have occurred in the Phase I study. Infusion related reactions are known to occur with the administration of monoclonal antibodies. These reactions consist of a symptom complex commonly characterized by fever and chills, but may also include other symptoms like nausea, vomiting, headache, and hypotension. Severe reactions may include among others bronchospasm, anaphylaxis, angioedema, and hypoxia. Infusion related reactions mostly occur during or immediately following the (initial) infusion.

Injection site reactions

A serious injection site reaction occurred in the Phase I study. For anthracycline treatments, which are also DNA-alkylating agents like SYD985, it is known that extravasation during the infusion may cause severe tissue lesions and necrosis. Although extravasation was not reported for the SYD985 case, it is recommended to avoid the use of veins over joints or in extremities with compromised venous or lymphatic drainage, like for anthracycline administration.

Immunogenicity

All biotherapeutics, including ADCs, have the potential to elicit a host immune response that can impact pharmacokinetics, efficacy and safety profiles. After administration of (ado-)trastuzumab emtansine, approximately 5% of the patients tested positive for anti-drug-antibodies (ADAs) but the clinical relevance of these antibodies is unknown. So far, none of the blood samples of the patients in the Phase I study was found positive for SYD985 ADAs at any time point and no clinical symptoms or pharmacokinetic profiles suggestive of the development of SYD985 ADAs have been observed.
In the study, blood samples will be drawn before every infusion to measure SYD985 ADAs.

Haematological toxicity
Transient, mostly mild or moderate, neutropenia, thrombocytopenia, and anemia have been noted in some patients in the Phase I study. Routine haematology (and biochemistry) assessments are frequently performed in the study and should be used to monitor haematological toxicities.

Skin toxicity
In the Phase I study, drug-related dry skin and skin hyperpigmentation have been reported. Patients are advised to limit sun exposure by using protective clothing and/or sun screen. In vitro studies showed that UV radiation did not markedly enhance the cytotoxic potential of the toxin SYD986.

Embryo-fetal toxicity
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 the clinical study. Participating patients must use two methods of effective contraception. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity. In case a patient becomes pregnant during SYD985 treatment, she must be discontinued from the study.

5.5.2 Physician's choice treatment

For safety considerations on the physician's choice treatments the information as described in the local Summary of Product Characteristics/Prescribing Information (SmPC/PI) of the specific treatments should be consulted. SYD985.002 is a global study and details may differ per country, therefore the investigator should consult the SmPC/PI as approved by their local country medicines agency (e.g. FDA, EMA, MHRA etc.). The local SmPC/PI will be provided and is to be filed in the ISF.

When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation, all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. If, for example, based on information in the medical history or the laboratory values of the patient one of the treatment options in the physician's choice group is contraindicated, that particular patient would have only three options of physician's choice treatment. Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.

During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

This protocol cannot address every safety consideration for all of the 'physician's choice' options. The investigator is referred to respective local summaries of product characteristics or prescribing information for specific guidance. In particular it is noted that there is variation among the options with regard to:

- duration of contraception after the last of study therapy administration;
- duration to avoid live vaccines before, during, and after study therapy administration;
- drug-drug interactions, in particular with regard to cytochrome P450 system.

5.6 Benefit – Risk assessment

Based on the Phase I experience it can be concluded that there is a positive benefit/risk for patients with late-line HER2-positive locally advanced or metastatic breast cancer who have had progression either during or after at least two HER2-targeting treatment regimens in the locally advanced or metastatic setting or after (ado-)trastuzumab emtansine treatment in the locally advanced or metastatic setting. Therefore, SYD985 represents a reasonable treatment option for the intended patient population in this study.

6 Objective(s)

6.1 Efficacy objectives

6.1.1 Primary objective

The primary objective of this study is to demonstrate that SYD985 is superior to physician's choice in prolonging PFS on the basis of the blinded independent central review of tumour assessments.

6.1.2 Secondary objectives

The secondary objectives of this study are to compare the two treatment groups with respect to:

- Overall survival (OS);
- Objective response rate (ORR) on the basis of the blinded independent central review;
- Investigator assessed PFS;
- Patient reported outcomes for health related quality of life;
- Safety and tolerability.

6.1.3 Other objectives

The other objectives of this study are as follows:

- To describe time to response in each treatment group;
- To describe duration of response in each treatment group;
- To describe the clinical benefit rate (CBR) in each treatment group;
- To evaluate the pharmacokinetics of SYD985;
- To evaluate the formation of SYD985 anti-drug antibodies (ADAs);
- To explore exposure/response and exposure/safety relationships.

7 Study design

This study is designed as a randomized, active-controlled, superiority study in patients with unresectable locally advanced or metastatic HER2-positive breast cancer. The patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment.

Eligible patients will be randomly assigned in a 2:1 ratio to receive SYD985 1.2 mg/kg infusions every three weeks or a combination treatment of physician's choice in a 21-day regimen. Patients will remain on study treatment until investigator-assessed disease progression, unacceptable toxicity or study termination by the Sponsor. After discontinuation of study treatment patients will be followed for survival until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor.

The study will end when:

- All patients have completed the treatment discontinuation visit, or
- Sufficient survival follow-up information is obtained to enable analysis, or
- The trial is terminated by the Sponsor.

When the study is ended before all patients have discontinued study treatment, individual patients who benefit from SYD985 treatment will be enabled to receive further SYD985 treatment.

8 Study Population

The study population will consist of patients with HER2-positive unresectable locally advanced or metastatic breast cancer. 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. Waivers to include patients that do not fully comply with the inclusion and exclusion criteria will not be granted.

Patients will be recruited from the investigator's general practice or via referral networks.

8.1 Eligibility Criteria

When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.

8.1.1 Inclusion Criteria

Any patient must meet the following inclusion criteria:

1. Female patients, age ≥ 18 years old at the time of signing informed consent;
2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;

3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component, or patients who have bone-only metastases requiring endocrine therapy or patients with non-visceral metastases requiring endocrine therapy, are not eligible;
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;
7. Estimated life expectancy > 12 weeks at randomization;
8. Adequate organ function, evidenced by the following (local) laboratory results:
   - Absolute neutrophil count ≥ 1.5 x 10^9/L;
   - Platelet count ≥ 100 x 10^9/L;
   - Hemoglobin ≥ 9.0 g/dL;
   - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN);
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases);
   - Serum creatinine ≤ 1.5 x ULN;
9. For women of childbearing potential two methods of effective contraception must be used during the study and up to 6 months after last study treatment. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity.

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. SYD985 at any time;
   b. Anthracycline treatment within 12 weeks prior to randomization;
   c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to randomization;
   d. Radiotherapy within 2 weeks prior to randomization;
   e. Hormone therapy within 1 week prior to randomization;

   The patient must have sufficiently recovered from any treatment-related toxicities to NCI CTCAE Grade ≤ 1 (except for toxicities not considered a safety risk for the patient at the investigator's discretion);
2. History of infusion-related reactions and/or hypersensitivity to trastuzumab, (ado-)trastuzumab emtansine or excipients of the study drug which led to permanent discontinuation of the treatment;
3. History of keratitis;

4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;
5. Left ventricular ejection fraction (LVEF) < 50% as assessed by either echocardiography or multigated acquisition (MUGA) scan at screening, or a history of clinically significant decrease in LVEF during previous treatment with trastuzumab or (ado-)trastuzumab emtansine leading to permanent discontinuation of treatment;
6. Cardiac troponin value above the ULN (local laboratory) at screening;
7. History (within 6 months prior to randomization) of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, treatment for brain metastases within 8 weeks prior to randomization. Patients with prior treatment of brain metastasis must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;
9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
10. Known active Hepatitis B or C infection;
11. Major surgery within 4 weeks prior to randomization;
12. Pregnancy or lactation;
13. Other condition, which in the opinion of the investigator, would compromise the safety of the patient or the patient's ability to complete the study.

8.2 Screen failures and re-screening

Patients who signed the “HER2 testing” and/or “Study”-ICF but subsequently failed to meet the inclusion and/or exclusion criteria are defined as 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. If a patient has clinically significant deviations in laboratory values as mentioned in inclusion criterion 8 and/or exclusion criterion 6 and/or clinically significant deviations in LVEF as detailed in exclusion criterion 5, it is not allowed to repeat the laboratory assessment and the patient cannot be randomized.

The only two exceptions are:

- If the result was HER2-negative based on archived material the site could consider sending fresh material to reassess the HER2 status.
- Patients for whom during screening on the brain CT/MRI a previously unknown asymptomatic metastasis is observed. These patients can be candidates for re-screening when the following conditions apply: (1) The treatment for brain metastases should be finalized more than 8 weeks prior to start re-screening; (2) There should be evidence of disease stability; (3) Enrolment for the SYD985.002 study should still be open. Please contact the medical monitor for approval. Note that for these patients all screening procedures should be repeated, excluding the central HER2-testing and the whole body bone scan if the previous scan showed no bone metastasis and there is no clinical suspicion of newly developed metastatic bone lesion(s).

9 Treatments

9.1 Treatment assignment, randomisation and stratification

After signing the "HER2 testing" or "Study"-ICF, the investigator (or authorized delegate) will enter the electronic Case Report Form (eCRF) to obtain a patient number. The eCRF will be provided by an external vendor and detailed instructions will be made available through training sessions and/or in a separate manual, which is to be filed in the TMF and ISF.

When all screening data are available, including confirmation by the central laboratory on the HER2 status assessment, the patient can be randomized if the patient complies with all inclusion criteria and none of the exclusion criteria.

A patient should be randomized within 28 days of signing the "Study"-ICF. To be able to randomize a patient, the investigator (or authorized delegate) should complete the required screening information in the eCRF. The randomization will be performed in the eCRF (Rave Balance module), detailed instructions will be made available through training sessions and/or in a separate manual, which is to be filed in the TMF and ISF. Randomization should be done on the day of first treatment or the day before if this turns out to improve logistics.

Using a computer-generated randomization list, eligible patients will be randomly assigned in a 2:1 ratio to receive SYD985 or Physician's choice therapy. The allocation will be stratified for geographical region (Europe and Singapore, North America), the number of prior treatment lines for advanced breast cancer (excluding hormone therapy) (1 or 2, more than 2), and prior treatment with pertuzumab (yes, no).

9.2 Description of Study Drug

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

Reference therapy	
Reference Product:	Physician's choice therapy: • Option 1: Lapatinib + Capecitabine • Option 2: Trastuzumab + Capecitabine • Option 3: Trastuzumab + Vinorelbine • Option 4: Trastuzumab + Eribulin The choice of reference therapy will be at the investigator's discretion and should be in accordance with local clinical practice.

9.3 Labeling, packaging and storage

9.3.1 SYD985 treatment

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, 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.

9.3.2 Physician's choice treatment

Commercial available reference therapy medication will be obtained directly by the site/affiliated pharmacy or provided by a local distributor for use during this study.

Once these drugs are allocated to the patient for use in this study it will be considered study drug. If required by local regulations labelling of the physician's choice treatment will be performed according to the Pharmacy Manual.

For details regarding packaging, handling, and storage the Summary of Product Characteristics and local Prescribing Information of these drugs should be followed.

9.4 Treatment regimen and individual administration procedure

9.4.1 SYD985 treatment

SYD985 1.2 mg/kg will be administered every three weeks (± 3 day) by intravenous infusion.

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 be used immediately or can be temporarily stored (see below).

The volume of the SYD985 solution needed for a particular patient should be calculated based on the weight of the patient. Weight measured on Cycle 1 Day 1 (or max 7 days earlier) should be used for the preparation of the infusion bag throughout the study. However, 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 an 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.

For the infusions an infusion set with a filter as specified in the pharmacy manual should be used.

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.

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 interruption of infusion will be discontinued from study treatment.

9.4.2 Physician's choice treatment

Physician's choice therapy options:

- Option 1: Lapatinib + Capecitabine
- Option 2: Trastuzumab + Capecitabine
- Option 3: Trastuzumab + Vinorelbine
- Option 4: Trastuzumab + Eribulin

The choice of reference therapy will be at the investigator's discretion and should be in accordance with local clinical practice. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

9.5 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.

9.5.1 SYD985 treatment

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 will be discontinued from study treatment and will be followed for survival follow-up as described in Section 11.22.

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.

As indicated in Section 9.4.1 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 interruption of infusion will be discontinued from study treatment.

Protocol requirements for specific toxicities are outlined below.

9.5.1.1 SYD985 - 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.

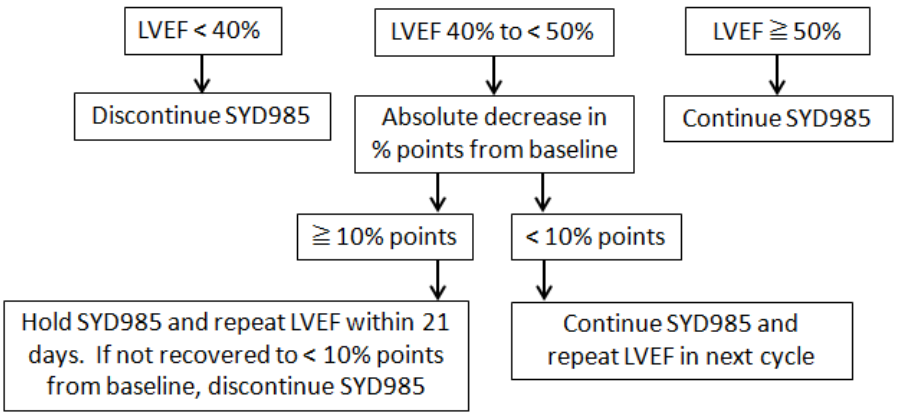

Figure 1: SYD985 dose modification based on LVEF measurements

SYD985 administration may be delayed to maximally 42 days after the last dose. Cardiac troponin values I or T (cTnI or cTnT) should also be taken into account for the final decision if a patient can continue or not.

9.5.1.2 SYD985 Dose modifications for eye toxicity

Patients who experience Grade 3 (or higher) keratitis will be discontinued from treatment. For patients who experience Grade 3 conjunctivitis, dosing must be delayed for up to 42 days from the last received dose. When the conjunctivitis 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.

9.5.1.3 SYD985 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.

9.5.1.4 SYD985 - Dose modifications for ILD/pneumonitis

Patients who experience Grade 2, 3 or 4 ILD/pneumonitis 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 IDL/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug-induced ILD/pneumonitis. ILD/pneumonitis evaluation (regardless of stage) should always include a pulmonary consult, a high resolution CT, PFTs, pulse oximetry and ABGs.
To detect ILD/pneumonitis or other pulmonary toxicity in an early stage, the tumour evaluation CT scans should be carefully evaluated for lung changes e.g. by means of high resolution CT. Infectious and metastatic disease-related aetiologies should be ruled out. Patients should be advised to promptly report any new or worsening respiratory symptoms. 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.

9.5.2 Physician's choice treatment

During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

Dosing of physician's choice treatments can be modified (reduced, delayed) according to local clinical practice.

If one of the two agents of the combination regimen is discontinued the therapy can be continued with a single agent. However, if both agents of the regimen are discontinued for more than 42 days from the last dose the patient will be considered to have discontinued treatment.

9.6 Treatment Compliance and accountability

All study drugs (SYD985 and physician's choice treatment) 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 according to the instructions provided in the Pharmacy Manual. 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 CRA.

9.6.1 SYD985 treatment

SYD985 will be administered to the patient by trained staff of the study site. Details of preparation and administration will be documented in the eCRF.

At the end of the study all unused SYD985 vials must be returned for destruction according to instructions specified in the Pharmacy Manual.

9.6.2 Physician's choice treatment

Depending on the physician's choice treatment regimen the study drug will be administered to the patient and/or dispensed to the patient by trained staff of the study site.

Details of preparation, administration and/or dispensing will be documented in the eCRF.

In the site drug accountability forms the following details on the physician's choice treatment will be documented:

- Brand name and international non-proprietary name (INN);
- Batch number;
- Dose and administration route;
- Each dose administered (for drugs administered on site);
- Number of doses administered (for drugs self-administered by the patient).

At the end of the study all unused physician's choice treatment dispensed to patients should be returned for accountability and destroyed according local hospital procedures.

9.7 Subject Emergency Card

At start of treatment patients will be handed out a Subject Emergency Card (See Appendix 1). 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 end of the study, i.e. upon completion or premature discontinuation, the patient is to return the Subject Emergency Card.

10 Pretreatment and concomitant medication and non-drug therapies

Information on all prior received anticancer therapies must be recorded in the eCRF. Washout criteria apply for prior anticancer therapy as described in exclusion criterion 1. Other pre-treatment medication and concomitant medication used between 14 days prior to signing "Study"-ICF till the treatment discontinuation visit should be recorded in the eCRF. 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.

Patients are allowed to receive supportive care therapies concomitantly during the study. Patients who receive anthracycline treatment within 12 weeks prior to randomization are not allowed to participate in the study. No other chemotherapy, immunotherapy, or experimental medications are permitted from 4 weeks prior to randomization, radiation therapy from 2 weeks prior to randomization, and 1 week for hormone therapy, during study treatment and (if possible) up to 30 days after the last study treatment dose.

During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed with regards to co-medications that are contraindicated or are to be used with precaution.

During study treatment and up to 30 days after the last treatment dose palliative radiotherapy is allowed only for the symptomatic treatment of painful bone lesions identified at baseline. Please contact the Medical Monitor for approval.

Patients who have disease control outside the brain, defined as having received clinical benefit (i.e. partial response (PR) or complete response (CR) of any duration, or stable disease (SD) for ≥ 4 months) but who have brain metastases that will benefit from treatment with radiation in the opinion of the investigator will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessment). Please contact the Medical Monitor for approval. Patients must not miss more than one 21-day cycle for the treatment of their brain disease to continue on therapy.

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 will be prescribed to patients in the SYD985 group, 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.

Patients of childbearing potential must use 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.[18] Acceptable forms of contraception include two of the following:

- Established use of oral, injected, implanted or other form of hormonal method of contraception;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Condom with spermicidal foam/gel/film/cream/suppository;
- Diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository.

The above contraception is not a requirement in the case of any of the following:

- Patient or sole partner of patient is surgically sterilized;
- True sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient).

Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods), progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action, and withdrawal are not acceptable forms of contraception.

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).

Visits are based on a 21-day (3-week) cycle (±3 days), with Cycle 1 beginning at Day 1. Assessments scheduled on the day of study drug administration should be performed prior to study drug administration unless otherwise noted.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all patients at each study site.

11.1 Obtain Informed Consent

At the screening visit, 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 ICF will be signed in duplicate and the patient and/or the authorised representative obtain one original of the signed ICF. The second original is filed with the study documents at the investigational site.

For potential eligible patients with archived tumour material available a "HER2 testing"-ICF may be used to allow the central assessment of HER2 tumour status. In case the patient's tumour HER2 status complies with inclusion criterion 4 the patient should sign the "Study"-ICF before full screening is started. The maximum time between signing the "HER2 testing"-ICF and "Study"-ICF is 28 days. In

case the patient's tumour HER2 status does not comply with inclusion criterion 4 there are two options. The first option is that the patient will not enter full screening. The second option is that the patient agrees to have a new biopsy taken for central HER2 status assessment. If a biopsy has to be performed to obtain tumour material for the central assessment of HER2 tumour status a patient will have to sign the "Study"-ICF. A patient may sign the "Study"-ICF without first signing the "HER2 testing"-ICF, in this situation assessment of HER2 tumour status will be part of the screening.

The patient should be randomized within 28 days of signing the "Study"-ICF.

11.2 Demographic 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), details on the hormone receptor (ER and/or PgR) status of the primary tumour and/or metastasis (if available), and classification of renal function and Child Pugh status.

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 at screening and treatment discontinuation, which will 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.

At all other visits, a targeted physical examination will be performed when indicated by the review of symptoms and AEs. Any AE should be reported in the eCRF.

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 should be measured at screening and at the time points as indicated in the flowchart (see Section 1.1). On Day1 of each cycle vital signs should be recorded before study drug administration.

Weight should be measured at screening and at the time points as indicated in the flowchart (see Section 1.1).
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 (see Table 1). It should be recorded at screening and at the time points as indicated in the flowchart (see Section 1.1). The ECOG performance status should be recorded before study drug administration on the Day1 visits.

Table 1: ECOG performance status[14]

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 Tumour material and central HER2 status assessment

Archival tumour material should be submitted to the central pathology laboratory during screening. If no archived tumour material is available a biopsy should be performed to obtain tumour material. If a biopsy needs to be performed this should be done before the screening scan for tumour evaluation according to RECIST is performed.

Tumour tissue samples should be submitted in the form of paraffin blocks. From submitted tumour blocks, a maximum of 10 slides will be cut at the central laboratory. The remaining part of the tumour block will be returned to the institution.

If due to local procedures it is not possible to submit a tumour block, 15 unstained freshly cut slides of 4 µm should be submitted. Preparation of tissue should be performed as detailed in the Central Laboratory Manual. The slides must be sent to the central laboratory within 2 days of being cut.

The HER2 tumour status (IHC and ISH) will be assessed by the central laboratory. A patient's HER2 status will be considered positive if the central laboratory reports grade 3+ staining intensity (on a scale of 0 to 3+) by means of IHC analysis and/or gene amplification by dual-signal ISH according to the ASCO-CAP criteria[15].

11.8 Haematology, blood chemistry, cardiac troponin, and urinalysis

Blood and urine samples will be taken at screening and at the time points as indicated in the flowchart (see Section 1.1). The samples will be analyzed by the local laboratory and central laboratory for haematology, blood chemistry, and cardiac troponin. The urinalysis will be performed locally.

The results of the local laboratory will be used for clinical decision making by the investigator in the daily practice. The results of the central laboratory will be used for the safety evaluation of lab parameters in the clinical study report (CSR).

The following parameters will be included:

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, reticulocytes.
Serum biochemistry:	Albumin, alkaline phosphatase, ALT, AST, total bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine kinase (CK), GGT, glucose, inorganic phosphorus, LDH, magnesium, potassium, sodium, total protein, uric acid.
Cardiac biomarkers:	cTnI or cTnT.
Urinalysis:	Dipstick for bilirubin, glucose, haemoglobin, ketones, and protein (microscopy if more than one parameter is positive).

Sampling should be done at screening and during treatment 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 8 or exclusion criterion 6 are not eligible to enter the study (see Section 8.1). For dose modifications or treatment discontinuations based on abnormal laboratory values, see Section 9.5. 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. Any changes regarding the normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, the Sponsor must be provided with a copy of the certification and a tabulation of the applicable normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At the end of the study, local laboratory results and central laboratory results will not be reconciled.

11.9 Pregnancy test

To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and serum or urine pregnancy tests during treatment on Day 1 of each cycle (may be done up to 3 days before) and at the treatment discontinuation visit will be performed at the local laboratory.

Women of childbearing potential participating in this clinical study should be instructed to use adequate contraceptive barriers to prevent them from getting pregnant while using study drug (see also Section 10).

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.

11.10 Pharmacokinetics (PK)

Blood samples for PK will be taken in the SYD985 group only. Blood sampling should be done according to the instructions in the Central Laboratory Manual and following the PK sampling schedule (see Section 1.1). Samples will be analyzed by a central laboratory using validated assays.

Multiple analytes will be measured to characterize the PK of SYD985:

- Total SYD985, which includes SYD985 with a drug-to-antibody ratio (DAR) of ≥ 0;
- Conjugated SYD985, which includes SYD985 with a DAR of ≥ 1;
- Free toxin (DUBA, SYD986).

One or two spare aliquots will be stored per time point for re-analysis purpose, a DAR average assay (if considered relevant and feasible), and/or other exploratory PK, biotransformation / metabolite identification or mode of action related assays which may turn out to be useful for further development of duocarmycin-based ADCs.

In case PK, immunogenicity, efficacy and/or safety data indicate a possible development of SYD985 ADAs, the Sponsor may discuss an intensified PK and/or immunogenicity sampling scheme with the sites on a case-by-case basis.

11.11 Immunogenicity

Blood samples to asses SYD985 ADAs will be taken in the SYD985 group only. Blood sampling should be done according to the instructions in the central laboratory manual and following the immunogenicity sampling schedule (see Section 1.1). Blood samples should be taken prior to SYD985 infusion, to avoid high concentrations of SYD985 which can influence the immunogenicity assessments. Samples will be analyzed by a central laboratory using validated assays.

Samples will first be screened for immune responses and in case of a positive response, further testing will be done in a confirmatory assay. If confirmed positive, the titer will be determined and the neutralizing ability of the SYD985 ADAs will be determined. The measurement of the neutralizing ability may be performed after the study has been completed.

In addition to the above described tests exploratory measurements for epitope mapping may be performed in the samples which are confirmed positive. These measurements may be performed after the study has been completed and possibly only in a selection of patients based on clinical data.

One or two spare aliquots will be stored per time point for re-analysis purposes, and/or other exploratory assays which may turn out to be useful for further development of duocarmycin-based ADCs.

In case PK, immunogenicity, efficacy and/or safety data indicate a possible development of anti-SYD985 antibodies, the Sponsor may discuss an intensified PK and/or immunogenicity sampling scheme with the sites on a case-by-case basis.

11.12 Serum HER2 ECD levels

Blood sampling to assess serum HER2 ECD levels should be done according to the instructions in the central laboratory manuals and following the sampling schedule (see Section 1.1). Blood samples

should be taken prior to study drug administration. Samples for serum HER2 ECD levels will be stored at a central laboratory. If indicated by the clinical safety or efficacy data and/or new scientific data the samples will be analyzed by a central laboratory. These measurements may be performed after the study has been completed and possibly only in a selection of patients based on clinical data.

11.13 Circulating tumour DNA

Blood sampling for exploratory measurements of circulating tumour DNA (ctDNA) should be done according to the instructions in the central laboratory manuals and following the sampling schedule (see Section 1.1). Blood samples should be taken prior to study drug administration. Samples for ctDNA will be stored at a central laboratory. If indicated by the clinical safety or efficacy data and/or new scientific data the samples will be analyzed by a central laboratory. To interpret data, it may be needed to also analyse the germline DNA. These measurements may be performed after the study has been completed and possibly only in a selection of patients based on clinical data.

11.14 Ophthalmological examination

At screening and the time points indicated in the flow chart (Section 1.1) an ophthalmologist (or qualified delegate) of the investigational site should perform an eye examination, which will include a slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry. Results of the examinations should be documented in the patient's medical chart and the eCRF.

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.

11.15 LVEF assessment

At screening and the time points indicated in the flow chart (Section 1.1) LVEF will be measured. If LVEF is below 50% the next assessment should be performed the next cycle as indicated in the dose modification Section 9.5.1.1.

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.

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.

11.16 ECG assessment

At screening and the time points indicated in the flow chart (Section 1.1) standard digital 12-lead ECG will be recorded in supine position after the patients being 5 minutes at rest. ECGs should be recorded with the ECG machine provided for the study.

ECGs should be recorded in triplicate for at least 3 seconds at each of the time points indicated in Table 2 with approximately a 3-5 minutes gap between each of the triplicate readings.

ECGs will be evaluated locally and centrally. The ECGS should be submitted to the Central ECG Centre according to the instructions in the Cardiology Manual.

The investigator or qualified delegate will evaluate the ECG at site and determine whether there are any abnormalities, and whether those abnormalities are clinically significant and need to be reported as (S)AEs and/or would lead to interruption/discontinuation of the treatment.

The Central ECG Centre will evaluate the ECGs and send the results to the site. The key parameters, including the QT/QTc interval, will be recorded in the eCRF. If new safety information is provided this should be included in the eCRF.

Table 2: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration[#]
3	Day 1: Before study drug administration[#]
4	Day 1: Before study drug administration[#]
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
Every subsequent 4th cycle	Day 1: Before study drug administration[#]
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine.

[#]For patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2 hours) after the Cycle 4 Day 1 ECG.

11.17 Tumour evaluation

Measurable and non-measurable lesions must be documented at screening (within 28 days of randomization) and must be re-assessed at each subsequent tumour evaluation. Tumour response will be assessed locally and centrally according to RECIST version 1.1 until disease progression (for details see Appendix 2).

The independent central review of tumour assessment scans will not determine eligibility or patient's treatment. All treatment decisions will be made by the investigator using local assessments.

Patients must have measurable or non-measurable disease that is evaluable per RECIST v1.1 (see Appendix 2) to be eligible for the study.

The tumour evaluation examinations at the visits indicated in the flowchart should include the scans as described below and as indicated in table 3:

- CT (or MRI) scan of the chest, abdomen, and pelvis (including liver, spleen, and adrenals), should be performed at screening, in-treatment visits and at the treatment discontinuation visit.
- CT (or MRI) scan of the brain at screening. It should be repeated in the event of clinical suspicion of progression of existing brain lesions and/or the appearance of new brain lesions.
- A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)) at screening. Skeletal lesions identified on the whole body bone scan at screening, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at screening and followed at scheduled visits using localized CT, MRI or X-ray. Whole body bone scan should be repeated in the event of clinical suspicion of the appearance of new bone lesions.
- Colour photography, including a metric ruler to estimate the size of the lesions, must be acquired for all skin lesions present (if not evaluable by imaging) according to the instructions in the imaging manual at screening. These should be followed throughout the study according to the schedule outlined in Table 3.

Table 3. Tumour imaging schedule

Procedure	**Screening**	**In treatment**	**Treatment discontinuation***
CT/MRI chest, abdomen, pelvis	Mandated	Every 6 weeks during the first 42 weeks and every 9 weeks thereafter	Mandated
CT/MRI of brain	Mandated	As clinically indicated	As clinically indicated
Whole body bone scan	Mandated	As clinical indicated	As clinically indicated
Localized bone X-ray/ CT/MRI	Only if skeletal abnormalities identified by whole body bone scan at screening, which are not visible in the chest, abdomen, pelvis CT/MRI	If bone lesion was present at screening, every 6 weeks during the first 42 weeks and every 9 weeks thereafter	Mandated only if bone lesion at screening
Skin colour photography	Only if skin lesions present at screening (if not evaluable by CT/MRI)	If skin lesion was present at screening every 6 weeks during the first 42 weeks and every 9 weeks thereafter or if clinically indicated	Mandated only if skin lesion was present at screening or if clinically indicated

*Tumour evaluation at the treatment 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 visit.

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 within 7 days of the assessment. Preferably the same investigator/radiologist should assess all tumour responses for each patient.

CT or MRI scans that were performed before a patient signed "Study"-ICF may be used to provide screening tumour status as long as they were performed within 28 days prior to randomization, 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.

In-treatment tumour assessments will be performed every 6 weeks (± 3 days) after the date of randomization, for the first 42 weeks and every 9 weeks (± 3 days) thereafter. The timing of the tumour assessments is independent of changes to the study treatment schedule e.g., dosing delays. 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 randomization.

In cases where there is a suspicion of progression before the next scheduled assessment an unscheduled assessment is to be performed. The reason for the unscheduled assessment should be reported on the eCRF.

At the end of the study, local tumour evaluation results and independent central review tumour evaluation results will not be reconciled.

11.18 Quality of life questionnaire

At the time points indicated in the flow chart (Section 1.1) all patient will complete the EORTC QLQ-C30 questionnaire (version 3) and the EORTC QLQ-B23 breast cancer specific module. The general questionnaire contains 30 questions and the breast cancer specific module 23 questions. Both questionnaires are validated for use in cancer patients participating in clinical studies.

11.19 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 "Study"-ICF till the treatment discontinuation visit should be recorded in the eCRF. 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.

11.20 (Serious) adverse events

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

11.21 Treatment discontinuation

The treatment discontinuation visit should occur 4-6 weeks (28-42 days) after the last administration of study drug (SYD985, trastuzumab, vinorelbine, eribulin, lapatinib, or capecitabine, whichever is discontinued last) or before new anticancer treatment is initiated, whichever comes first.
See the flowchart (Section 1.1) for the assessments to be performed at the treatment discontinuation visit.

11.22 Survival follow-up

Every three months after the treatment discontinuation visit a survival follow-up visit (or phone call) should be scheduled. During this visit data will be collected on disease progression, unresolved AEs, new anticancer therapies, and survival. These survival follow-up visits should continue until patient's death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first.

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.
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	The following events are adverse events of special interest (AESIs) and will need to be reported to the CRO expeditiously, irrespective of regulatory seriousness criteria or causality: • ILD/Pneumonitis, • Severe eye toxicity grade ≥ 3, • Keratitis grade ≥ 2, • LVEF decrease to < 50%.

12.2 Adverse event monitoring

During the study safety assessments will include physical examination, ECOG performance status, vital signs, weight assessment, ECG, LVEF measurements, laboratory measurements (haematology, chemistry, cardiac biomarkers, SYD985 ADA levels), urinalysis, ophthalmological examination, and AE reporting.

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 "Study"-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 "Study"-ICF up to the treatment discontinuation visit. Events present before signing of the informed consent will be defined as medical history of the patient

participating in the study. 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 12.3.1 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 disease 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 will determine the severity of AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03). AEs that are not listed in the CTCAE should be graded according to Table 4.

Table 4: Adverse Event grading (for events not listed in the NCI CTCAE)

Grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated, although this could improve the overall well-being or symptoms of the subject.

Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death.

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 fulfil this definition.

12.4 Serious Adverse Events Documentation

All SAEs and must be documented on an SAE Reporting Form. The following information must be provided:

- 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;
- Results of rechallenge (if applicable);
- 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.

Hospitalizations due solely 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 SAEs from signing of the "Study"-ICF up to the treatment 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 by telephone, fax or email. The notification must include a completed SAE form. The contact details of the [redacted] Pharmacovigilance Department are:

Pharmacovigilance Department [redacted]
Address: [redacted]

Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [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 in the form of a follow-up report 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 CRF and to the [redacted] Pharmacovigilance Department.

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 section 6.8 of the Investigator's Brochure contains the reference safety information and is to be used to assess the expectedness of an AE for SYD985. The reference Summary of product characteristics is to be used to assess expectedness for Physician's choice treatments.
Investigators must report all SAEs to their Independent Ethic Committee (IEC)/ Institutional Review Board (IRB) responsible for the study. In addition, in case of a SUSAR occurring in a patient treated with Physician's Choice treatment the investigator is responsible for reporting the SUSAR to the respective manufacturer.

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;
- Severe eye toxicity grade ≥ 3;
- Keratitis grade ≥ 2;
- LVEF decrease to < 50%.

All AESIs must be documented on an SAE Reporting Form and the same details need to be reported.

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.

The occurrence of any AESIs, from signing of the "Study"-ICF up to the treatment discontinuation visit (regardless of relationship to study drug) has to be notified (within 5 days of the investigator or designee becoming aware of the event) to the CRO by telephone, fax or email. The notification must include a completed SAE form. If a SAE occurs in conjunction with the AESI, then the reporting time frame for an SAE (24 hours) must be met.

The contact details of the [redacted] Pharmacovigilance Department are:
Address: [redacted]
Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [redacted]

The investigator or designee must report (within 5 days of becoming aware of the event) clinically significant follow-up information pertaining to the AESI in the form of a follow-up report 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 AESI has to be reported in the CRF and to the [redacted] Pharmacovigilance Department.

12.7 Reporting of Death

Deaths that occur during the protocol-specified AE reporting period (from signing of the "Study"-ICF up to the treatment discontinuation visit) that are, according to the investigator, due solely to the progression of underlying malignancy, should not be recorded as an AE. These deaths should be recorded only on the Study discontinuation eCRF or if the patient already discontinued treatment due to another reason on the Survival follow-up eCRF.

All other deaths that occur during the protocol-specified AE reporting period should be recorded on an SAE eCRF and expeditiously reported.

During post-study survival follow-up, deaths due to any cause should be recorded on the Survival follow-up 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 case a UK site is participating in the study, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK should be notified according to their guidance. The CRO should notify the MHRA, on behalf of the Sponsor, within 7 days of becoming aware of the breach and investigate and take action simultaneously or after the notification.

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.

12.10 Data Monitoring Committee

Details on the responsibilities, activities and deliverables of the external Data Monitoring Committee (DMC) are detailed in a separate charter. As part of their evaluation the DMC assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis.

13 Criteria 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:

- Progressive disease;
- Unacceptable toxicity, including:
  - Clinically significant symptomatic cardiac disease (see Section 9.5.1.1);
  - 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 IDL/pneumonitis;
- Pregnancy;
- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest.

Patients who discontinue from study treatment for any of the above reasons should return to the clinic for a treatment discontinuation visit 4-6 weeks (28-42 days) after the last administration of study drug (SYD985, trastuzumab, vinorebine, eribulin, lapatinib or capecitabine, whichever is discontinued last). Subsequently, these patients will continue to be followed according to protocol for disease progression, unresolved AEs, new anticancer therapies, and survival status as detailed in Section 11.22.

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 Completion

A patient is considered to have discontinued study treatment when study treatment is permanently discontinued due to any reason.

A patient is considered to have discontinued the study if the patient is lost to follow-up or withdrew consent or another reason exists that prevents additional data to be collected on the patient.

A patient is considered to have completed the study when the patient has died while still in the study.

13.3 Patient replacement

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

13.4 Study termination

The clinical study may be stopped 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 addition, further recruitment may be stopped 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 medical, ethical, or business reason.
In such case, all patients will be requested to return to the clinic for a final follow-up visit, during which all medication will need to be returned (if applicable) and 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.

The Sponsor decides when to stop collection of survival follow-up data, which should be at least after all patients in the SYD985 group discontinued treatment and completed the treatment discontinuation visit (if possible) or were lost to follow-up, in order to finalize data analysis. This will be communicated to the participating clinical sites.

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 at least before completion of study enrolment. 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 9.3 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 (%).

All data from all clinical assessments will be presented in listings.

14.2 Analysis Populations

14.2.1 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment they actually received. Treatment actually received is defined as the study treatment (SYD985 or Physician's choice) the patient receives on Cycle 1 Day 1.

14.2.2 Full analysis Set

The Full Analysis Set (FAS) comprises all randomized patients. Following the intent to treat (ITT) principle, patients will be analyzed according to the treatment group and strata they have been assigned to during the randomization procedure. The FAS will be the primary population for all the efficacy analyses.

14.2.3 Per-Protocol Set

The Per-Protocol Set (PPS) will include the subset of the patients in the FAS who were administered at least one dose of study medication and who do not have any major protocol deviations or multiple minor deviations. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the SAP. Patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. Sensitivity analysis of the primary endpoint of PFS will be performed using PPS.

14.3 Study endpoints

14.3.1 Primary endpoint

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

Data for patients without disease progression or death from any cause as of the data cut-off date will be censored at the time of the last tumour assessment with an outcome other than "unevaluable" or, if no tumour assessment was performed after the baseline visit, at the time of randomization plus 1 day. Data for patients without disease progression or death from any cause as of the date when a new therapy for cancer is started will be censored at the time of the last tumour assessment with an outcome other than "unevaluable" or, if no tumour assessment was performed after the baseline visit, at the time of randomization plus 1 day.
Data from patients who are lost to follow-up will be included in the analysis as censored observations on the last date of tumour assessment that the patient was known to be progression free. Data from patients whose disease progression or death occurs after two or more consecutive missed tumour assessment will not be counted. In these cases, the patient will be censored at the patient's last tumour assessment prior to the missing assessment. If disease progression occurs after one missed tumour assessment, the event will be counted at the respective event date (details will be in the SAP).

14.3.2 Secondary endpoints

The secondary efficacy endpoints are:

- Overall Survival;
- Objective Response Rate on the basis of the blinded independent central review;
- Investigator assessed PFS;
- Patient reported outcomes for health related quality of life.

Overall Survival (OS) is defined as the time from date of randomization 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 randomization plus 1 day.

Objective Response Rate (ORR) is defined as the proportion of patients with ICR-assessed best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1. Only patients with measurable disease at baseline will be included in the analysis of ORR. Patients without a post-baseline tumour assessment will be considered non-responders.

Investigator assessed PFS is defined as the time from the date of randomization 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.

Patient reported outcomes for health related quality of life are collected with the EORTC QLQ-C30 questionnaire along with the disease-specific breast cancer module (EORTC QLQ-BR23). Scoring of raw QoL data and methods for handling missing items or missing assessments will be handled according to scoring manuals for each respective patient questionnaire.

14.3.3 Other endpoints

- To describe time to response in each treatment group;
- To describe duration of response in each treatment group;
- To describe the CBR in each treatment group;
- To evaluate the pharmacokinetics of SYD985;
- To evaluate the formation of SYD985 ADAs;
- To explore exposure/response and exposure/safety relationships.

14.4 Demographic and baseline characteristics

Relevant demographic and baseline data will be summarized descriptively by treatment group using data from the FAS population and PPS population.

14.5 Efficacy analysis

14.5.1 Primary objective

The primary objective of the study is to demonstrate that SYD985 is superior to physician's choice, in prolonging PFS on the basis of blinded independent central review of tumour assessment.

14.5.1.1 Timing of analysis

The primary PFS analysis will be performed when at least 256 PFS events have occurred, as assessed by central review, or when at least 95% of patients have discontinued treatment, and only after all patients have been enrolled.

14.5.1.2 Analysis

Progression will be assessed via blinded independent central review according to RECIST 1.1. Progression as assessed through local radiology assessment will be used for supportive evidence of the primary efficacy analysis.

The primary efficacy endpoint PFS will be analyzed based on the data observed in the FAS population, according to the treatment group patients were randomized and the strata they were assigned at randomization. The stratification factors assigned at randomization are world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no). The survival distribution of PFS per treatment group will be estimated using the Kaplan-Meier method. The median PFS along with 95% CIs will be presented by treatment group.

The comparison of the survival distributions of PFS between the two treatment groups will be performed using a stratified log-rank test at the two-sided 5% level of significance, i.e.,

H_{01}: $S_{1T}(t) = S_{1C}(t)$ vs. H_{a1}: $S_{1T}(t) \neq S_{1C}(t)$, for all $t \geq 0$ (t=timepoint)

Where $S_{1T}(t)$ is the survival distribution function of PFS in the treatment group of SYD985 and $S_{1C}(t)$ is the survival distribution function of PFS in the reference treatment group (physician's choice).

or in words

H_{01}: there is no difference between the populations in the probability of an event (PFS) at any time point.
versus
H_{a1}: there is a difference between the populations in the probability of an event (PFS) at some time point.

A stratified Cox regression analysis will be used to estimate the HR of PFS, along with 95% CIs (using the same strata information as above).

14.5.1.3 Supportive analyses

Sensitivity analyses for the primary endpoint will be performed, particulars will be detailed in the SAP.

14.5.2 Secondary objective

The secondary objectives of this study are to compare the two treatment groups with respect to OS, ORR on the basis of the blinded independent central review and investigator assessed PFS.

14.5.2.1 Analysis

14.5.2.1.1 Overall Survival

The analysis for OS will be based on the FAS population. The following statistical hypothesis for OS will be tested:

H_{02}: $S_{2T}(t) = S_{2R}(t)$ vs. H_{a2}: $S_{2R}(t) \neq S_{2C}(t)$, for all $t \geq 0$ (t=timepoint)

Where $S_{2T}(t)$ is the survival distribution function of OS in the treatment group of SYD985 and $S_{2R}(t)$ is the survival distribution function of OS in the reference treatment group (physician's choice).

The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at two-sided 5% level of significance. The strata information will be based on the data obtained from the system that was utilized for randomization.

The first OS analysis will be performed at the time of the primary efficacy analysis of PFS. Subsequent analyses of the OS will be planned to support regulatory questions or scientific publications.

The survival distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% CIs will be presented by treatment group. The stratified Cox regression analysis will be used to estimate the HR of OS, along with 95% confidence interval.

In addition, the 1-year survival rate and corresponding 95% CI will be estimated using the Kaplan-Meier approach.

14.5.2.1.2 Objective response rate

ORR will be calculated based on the FAS population. Proportion of patients with ORR will be presented by treatment group along with 95% CIs. The Cochran-Mantel-Haenszel test (strata based on the baseline stratification factors) will be used to compare the two treatment groups with respect to the ORR at two-sided 5% level of significance.

As a supportive analysis, patients ORR as assessed by local radiology assessment will be calculated by treatment group and presented along with the 95% CIs.

14.5.2.1.3 Investigator assessed PFS

Investigator assessed PFS will be calculated based on the FAS population. The survivor distribution of PFS will be estimated per treatment group using the Kaplan-Meier method. The median PFS along with 95% CI will be presented by treatment group. A stratified Cox regression analysis will be used to estimate the HR of PFS, along with the 95% CI. The treatment groups will be compared using the 2-sided stratified log-rank test.

14.5.2.1.4 Patient reported outcomes

The number of patients completing each patient questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time points for the EORTC QLQ-C30 and EORTC QLQ-B23 questionnaires. The FAS will be used for analyzing the data.

Descriptive statistics will be used to summarize the scores scales for the EORTC questionnaires at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses.

The global health status/QoL scale score of the EORTC QLQ-C30 is identified as the primary patient-reported outcome variable of interest. Physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30, and the breast cancer symptoms scale score of the EORTC QLQ-BR23 are identified as secondary patient-reported outcome variables of interest. Analytic tests will be performed using parametric and non-parametric tests where necessary, further details will be provided in the SAP.

14.5.3 Other objectives

14.5.3.1 Time to response

Time to response is the time between the date of randomization until first documented response (CR or PR) according to RECIST 1.1. All patients will be included in time to response calculations. Patients who did not achieve a CR or PR will be censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed of death due to any cause) or at the date of last adequate tumour assessment date otherwise.
Time to response will be analyzed based on the data observed in the FAS population and will be determined primarily by independent central review of tumour assessment (an analysis based on investigator tumour assessment will also be performed). Time to response will be summarized for the two treatment groups using descriptive statistics.

14.5.3.2 Duration of response

Duration of response only 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).
Duration of response will be analyzed based on the data observed in the FAS population and will be determined primarily by independent central review of tumour assessment (an analysis based on investigator tumour assessment will also be performed). The censoring methods for this endpoint are similar to those described for PFS. The Kaplan-Meier approach will be used to estimate the median duration of response of each treatment group and the corresponding 95% CIs.

14.5.3.3 Clinical benefit rate

The CBR is defined as the proportion of patients with CR, PR, or SD (SD for 24 weeks (6 months) or longer). CR, PR and SD are defined according to RECIST 1.1. CBR will be analyzed based on the data observed in the FAS population and will be determined primarily by independent central review of tumour assessment (an analysis based on investigator tumour assessment will also be performed). CBR will be summarized for the two treatment groups using descriptive statistics.

14.5.3.4 Pharmacokinetic analysis

Observed concentrations for total SYD985 (including SYD985 with a drug-to-antibody ratio (DAR) ≥ 0), conjugated SYD985 with DAR ≥ 1, and for the free toxin (DUBA, SYD986) will be summarized for each specified PK sampling point. Non-compartmental, compartmental analysis and/or population PK approach will be used to analyze PK data if appropriate. The PK parameters for total SYD985, conjugated SYD985, and for SYD986 including, but not limited to, AUC, C_{max}, C_{min}, CL, V, $T_{1/2}$ will be reported as data allow and the inter-patient variability will be assessed.
The influence of patient covariates on PK will also be evaluated, further details will be given in the SAP.

14.5.3.5 SYD985 anti-drug antibody formation

The formation of SYD985 ADAs will be assessed. A separate ADA assessment plan will be prepared.

14.5.3.6 Exposure response analysis

If data allow, exploratory analysis or modeling techniques will be used to investigate the relationship between SYD985 exposure and safety/efficacy parameters (e.g. SYD985-related toxicity, PFS, and/or OS).

14.6 Safety data analysis

Safety analysis will be based on the SAF 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 and including treatment discontinuation visit. Events starting before first dosing will be presented separately.

14.6.1 Extent of exposure

The total cumulative dose, number of doses, dose intensity, and duration of exposure for the SYD985 and Physician's choice groups 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.

14.6.2 Treatments

Concomitant medication and non-drug therapies will be listed by patient and summarized by ATC (Anatomical therapeutic chemical classification system) term for each treatment group. These

summaries will include medications starting on or after the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

14.6.3 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 4.03)

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 by treatment group.

Separate summaries presented by treatment group will be given for all and 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 presented by treatment group will be given for all AESI categories and drug-related AESIs.

14.6.4 Clinical Laboratory Evaluations

Changes in laboratory data will be summarized by grade using the NCI CTCAE version 4.03 or higher for each treatment group. Changes from baseline will be presented in shift tables for the different lab assessments.

14.6.5 ECG analyses

Standard ECGs parameters (e.g. heart rate, PR, QRS, and QT) will be summarized by treatment group and scheduled visits. The number of patients who discontinue drug due to cardiac function will be summarized. Further cut-points might be analyzed if appropriate.

A separate ECG analysis plan will be prepared for a more detailed analysis of the ECGs including QTc interval analysis and exposure response analysis.

14.6.6 LVEF

Absolute LVEF measurements, as well as changes from baseline as a function of time, will be summarized by treatment group and 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. Further cut-points might be analyzed if appropriate.

14.6.7 Ophthalmological 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 treatment group and scheduled visits.

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

14.6.8 Other Safety Measures

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

14.7 Sample size

The primary efficacy endpoint of this study is PFS based on independent central review of tumour assessment. The primary efficacy analysis will be event driven.

In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 30% drop out in the physician's choice group and 40% in the SYD985 group, a minimal number of 423 patients is required. Allocation is 2:1 resulting in 282 to be allocated to the SYD985 group and 141 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

No formal interim analysis will be performed. As part of their evaluation the DMC assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rate. Such sample size re-estimation will not be considered a formal interim analysis as no between-group comparison of event-rates will be performed. Therefore, the primary analysis will be performed at the set 5% significance level. Details of methods used will be provided in a separate analysis plan.

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

The Sponsor/CRO will obtain regulatory approval from the competent authority prior to study start. The Sponsor/CRO will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtain approval is amended, the Sponsor/CRO will submit these documents for review and subsequent approval to the competent authority.

An annual safety/progress report will be provided by Sponsor/CRO to the competent regulatory authority.

15.1.2 Review and Approval by Competent IRB or IEC

The Sponsor or the Sponsor's representatives will obtain ethical approval from the competent IEC(s)/IRB(s) prior to study start. The Sponsor or the Sponsor's representatives will provide all necessary documents to obtain such approval.

If any of the documents relevant to obtain approval is amended, the Sponsor or the Sponsor's representatives will submit these documents for review and subsequent approval to the competent IEC(s)/IRB(s).

An annual safety/progress report will be provided by Sponsor/CRO to the competent IEC(s)/IRB(s) as required.

15.1.3 Informed Consent

Informed Consent will be obtained from the potential patient prior to any study-related activities and in accordance with local laws and all applicable regulatory requirements. For this study a specific "HER2 testing"-ICF may be used to allow the central assessment of HER2 status of available archived tumour tissue from patients who are interested to participate. This may avoid unnecessary study assessments and may speed up recruitment. The "Study"-ICF should be signed before full screening is started.

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. The patient or the authorised representative must complete the printed name and personally enter the date of signature. If an authorised representative signs the ICF, all efforts should be made to obtain an additional personally-dated signature from the patient herself.

The ICF will be signed in duplicate and the patient and/or the authorised representative obtain one original of the signed ICF. The second original is filed with the study documents at in the 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.

15.1.4 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).

15.1.5 Amendments to Study Protocol

Amendments to the study protocol are performed 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.

15.1.6 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.

15.1.7 Coordinating Investigator for Clinical Study Report

An interim CSR will be prepared by the Sponsor/CRO to describe the results of the study following the primary analysis, a final CSR will be prepared at the end of the study. One (or several) of the investigator(s) will be selected by the Sponsor to review and approve the 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 and Sponsor's/CRO's procedures, monitors from Sponsor/CRO will perform the monitoring of this study. Investigational sites will be contacted and visited regularly by Sponsor/CRO staff. The investigational sites will be trained on all study procedures at an investigator meeting and during site initiation visit.

During the study, the sites will be visited by Sponsor/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 Sponsor/CRO 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 Sponsor/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 Sponsor/CRO, 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, laboratory reports and X-rays. The nature of source data and requirement for its maintenance will be described in a separate Source Data Agreement with the investigator.

15.2.3 Quality Assurance

To ensure compliance with study protocol, ICH GCP, and applicable regulatory requirements, the Sponsor/CRO 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 human subject 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. On a regular basis medical safety monitoring meetings evaluating the accumulated safety data will be organized with the responsible persons from Sponsor/CRO. In addition, the accumulated protocol deviations will be evaluated and discussed on a regular basis by the responsible persons from Sponsor/CRO.

15.3 Data Handling and Records Retention

15.3.1 Collection of Data, 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.

For patients who fail screening, data are to be collected from the time the informed consent is signed until it is determined that the patient has failed the screening. An eCRF with minimum information is to be completed, including demographics, reason for screen failure and (serious) AEs.

The eCRFs must be kept in order and up-to-date so that they always reflect the latest observations on the patients enrolled in the study.

The signed original ICF(s) should be attached to the patient's medical chart. When the patient discontinued or completed the study, the signed ICF(s) should be kept with the printed copies of the eCRF, or a note made indicating where the consent form is located. All source data should be kept in conformance to applicable national laws and regulations.

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.

ECRFs must be completed for each patient enrolled in the study and signed-off by the investigator. This should be done as soon as possible after the patient discontinued or completed the study. A monitor will review the completed eCRF.

Data management will be performed by the Sponsor/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 Sponsor/CRO will 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 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.

16 References

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17 Appendices

Appendix 1 Sample Subject Emergency Card

Front:

Mrs:_____**Date of birth:**_____
(subject's first and last name) (ddMMMyyyy)

is participating in a clinical study with protocol number SYD985.002 entitled:
Multi-centre, open-label, randomized clinical trial comparing the efficacy and safety of the antibody-drug conjugate SYD985 to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer

[Study logo]

EudraCT number: 2017-001994-18 [where required in Europe]
IND number: 131333 [where required in US]

Subject number: _____ [subject's study identification number]

In case of an <u>emergency</u> please contact the following doctor:

_____
[Investigator's name and contact information]

[If applicable add other staff name and contact details, e.g. study coordinator]

Emergency number of medical monitor to be used by **<u>medical staff only</u>**:

_____
[Medical monitor name and telephone number]

(See reverse side)

Back:

Study medication: SYD985 or physician's choice
SYD985 is a duocarmycin-based HER2-targeting antibody-drug conjugate. SYD985 is an investigational drug and is in development for the treatment of breast cancer.
Physician's choice is one of the following 4 options: 1) Lapatinib + Capecitabine, 2) Trastuzumab + Capecitabine, 3) Trastuzumab + Vinorelbine , 4) Trastuzumab + Eribulin. All these drugs are used to treat breast cancer.

Please keep this card with you at all times and <u>return it at your final visit to the clinic</u>!

[If applicable add additional country/site specific text here, e.g. as required per authority/IEC/IRB]

Sponsor:
Synthon Biopharmaceuticals BV
Microweg 22
6545 CM Nijmegen
The Netherlands
[redacted]

Appendix 2 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 caliper 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. Leptomenngeal 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 measuarable (± 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 = inevaluable		

Evaluation of best overall response

The best overall response is the best response recorded from the randomization 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 inevaluable.

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 3 Protocol Amendment I

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment I (leading to Protocol Version 2.0)
Amendment Date:	25 August 2017
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared upon request of the regulatory authorities. The changes are summarized below:

- Inclusion criterion 3 on previous HER2-targeting treatment has been specified in more detail.
- Inclusion criterion 4 on HER2 status has been specified in more detail.
- An exclusion criterion on prior pulmonary disease has been added as criterion 9.
- Previous exclusion criterion 9 on HIV and hepatitis has been amended to allow the inclusion of HIV infected patients.
- Two additional time points (Cycle 2 Day 1 and Cycle 4 Day 1) for assessments of the QoL questionnaires have been added to the flowchart.
- The dose modification guidances for eye toxicity and pneumonitis have been adjusted.
- The ECG assessments requirements for the physician's choice group receiving Lapatinib + Capecitabine have been explained in more detail.
- In addition to Europe and North-America also sites in Singapore are planned to participate, this has been added.
- Details regarding the required infusion materials have been replaced by more general wording with reference to the pharmacy manual in which full details are described.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 2 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: Inclusion criteria (page 3) & Section 8.1.1 Inclusion criteria (page 24)

3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment;
4. HER2-positive tumour status (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;

Now reads as:

3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;

Protocol synopsis: Exclusion criteria (page 4) & Section 8.1.2 Exclusion criteria (page 25)

8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to randomization. Patients with prior treatment of brain metastases must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;
9. Known infection with HIV, or known active Hepatitis B or C infection;
10. Major surgery within 4 weeks prior to randomization;
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.

Now reads as:

8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to randomization. Patients with prior treatment of brain metastases must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;
9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
10. Known ~~infection with HIV, or known~~ active Hepatitis B or C infection;
11. Major surgery within 4 weeks prior to randomization;
12. Pregnancy or lactation;
13. Other condition, which in the opinion of the investigator, would compromise the safety of the patient or the patient's ability to complete the study.

Synopsis (page 4)

The calculated amount of solution should be added to an infusion bag containing 100 mL of 0.9% sodium chloride without other additives. If reconstituted vials or the prepared infusion bag is not used immediately, it can be stored at 2 to 8 °C (36-46 °F) for a maximum of 24 hours up to start of infusion.

Now reads as:

The calculated amount of solution should be added to an infusion bag containing ~~100 mL of~~ 0.9% sodium chloride without other additives. If reconstituted vials or the prepared infusion bag is not used immediately, it can be stored at 2 to 8 °C (36-46 °F) for a maximum of 24 hours up to start of infusion.

Protocol synopsis: Study assessments and procedures (page 5)

EORTC QLQ-C30 and breast module QLQ-BR23 questionnaires will be used every 2nd cycle to monitor changes in the patient's QoL.

Now reads as:

EORTC QLQ-C30 and breast module QLQ-BR23 questionnaires will be used on day 1 of the first 5 cycles and subsequently every 2nd cycle to monitor changes in the patient's QoL.

Section 1.1 Study flowchart (page 9)

10 Ophthalmological examination as well as LVEF assessment 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;

Now reads as:

10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;

Section 9.4.1 SYD985 treatment (page 28)

The required volume needs to be withdrawn from the vial(s) and added to a polyethylene (PE)-lined polyolefin infusion bag (e.g. Baxter Viaflo bag) containing 100 mL of 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.

For the infusions, a polyvinylchloride – trioctyl trimellitate (PVC-TOTM; e.g. From Codan) or polypropylene/polyurethane/silicone (PP/PUR/silicone; e.g. from Fresenius Kabi) infusion set with a 0.2-micron in-line polyethersulfone (PES) filter should be used.

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 up to 100 mL of sterile 0.9% sodium chloride solution for infusion, at the discretion of the investigator.

Now reads as:
The required volume needs to be withdrawn from the vial(s) and added to an ~~a polyethylene (PE)-lined polyolefin~~ infusion bag as specified in the pharmacy manual ~~(e.g. Baxter Viaflo bag)~~ containing ~~100 mL of~~ 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.

For the infusions an~~, a polyvinylchloride – trioctyl trimellitate (PVC-TOTM; e.g. From Codan) or polypropylene/polyurethane/silicone (PP/PUR/silicone; e.g. from Fresenius Kabi)~~ infusion set with a ~~0.2-micron in-line polyethersulfone (PES)~~ filter as specified in the pharmacy manual should be used.

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 ~~up to 100 mL of~~ sterile 0.9% sodium chloride solution for infusion as indicated in the pharmacy manual, at the discretion of the investigator.

Section 9.5.1.2 SYD985 Dose modifications for eye toxicity (page 31)
For patients who experience Grade 3 (or higher) keratitis or Grade 3 conjunctivitis, dosing must be delayed for up to 42 days from the last received dose. When the keratitis or conjunctivitis 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 will be discontinued from treatment. For patients who experience ~~Grade 3 (or higher) keratitis or~~ Grade 3 conjunctivitis, dosing must be delayed for up to 42 days from the last received dose. When the ~~keratitis or~~ conjunctivitis 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.

Section 9.5.1.4 SYD985 - Dose modifications for pneumonitis (page 31)
For patients who experience Grade 2 (or higher) pneumonitis dosing must be delayed for up to 42 days from the last received dose. When the pneumonitis resolves to Grade 1 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 pneumonitis persists. The pneumonitis should be monitored for recovery.

Now reads as:
Patients who experience Grade 3 or 4 pneumonitis will be discontinued from treatment. For patients who experience Grade 2 ~~(or higher)~~ pneumonitis dosing must be delayed for up to 42 days from the last received dose. When the pneumonitis resolves to Grade 1 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 pneumonitis persists. The pneumonitis should be monitored for recovery.

Section 11.16 ECG assessment (page 40)
Table 5: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration
4	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*

	Day 2: 24 hours after study drug administration (±2 hours)
Every subsequent 4th cycle	Day 1: Before study drug administration[#]
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving Lapatinib + Capecitabine.

Now reads as:

Table 6: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration[#]
4	Day 1: Before study drug administration[#]
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)[#]
Every subsequent 4th cycle	Day 1: Before study drug administration[#]
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving Lapatinib + Capecitabine.

[#]For patients in physician's choice group receiving Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1 and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2hours) after the Cycle 4 Day 1 ECG.

Appendix 4 Protocol Amendment II

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment II (leading to Protocol Version 3.0)
Amendment Date:	09 November 2017
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared upon request of the regulatory authorities. The changes are summarized below:

- The flowchart has been updated to add pregnancy tests on Day 1 of every cycle and at the treatment discontinuation visit.
- The flowchart has been updated to add an ECG assessment at Cycle 3 Day 1.
- A total of 5 protocol sections have been updated to re-iterate and emphasize the importance to follow the SmPC guidance for patient selection and management in the physician's choice group.
- A section on the benefit/risk ratio has been added.
- In relation to cardiotoxicity it has been added that clinically relevant electrolyte disturbances should be corrected.
- The possibility to enable further SYD985 treatment when the study has ended is added.
- The indicated contraception has been updated to be aligned with the CTFG recommendations.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 3 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: Study population (page 3)
The study population will consist of patients with HER2-positive unresectable locally advanced or metastatic breast cancer complying with the following in- and exclusion criteria:
Inclusion criteria

1. Female patients, age ≥ 18 years old at the time of signing informed consent;
2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;
3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic componentare not eligible;
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

Now reads as:

When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per Summary of Product Characteristics/Prescribing Information for the physician's choice treatment options, should be taken into account. **Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.**

The study population will consist of patients with HER2-positive unresectable locally advanced or metastatic breast cancer complying with the following in- and exclusion criteria:

Inclusion criteria

1. Female patients, age ≥ 18 years old at the time of signing informed consent;
2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;
3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;
4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH)) confirmed by the central laboratory;
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component, or patients who have bone-only metastases requiring endocrine therapy or patients with non-visceral metastases requiring endocrine therapy, are not eligible;
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

Section 1.1 Study flowchart (page 8)

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 "Study"-ICF an eligible patient should be randomized within 28 days. A "HER2 testing"-ICF may be used to assess the HER2 tumour status on archival tumour tissue to determine patient eligibility;
2. Day 1 assessments are to be done prior to study drug administration;
3. Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4. Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5. Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6. Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7. Pregnancy test in women of childbearing potential: serum test at screening, urinary tests during treatment in case of suspected pregnancy;
8. PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9. Immunogenicity samples will be taken in the SYD985 group only;
10. Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11. 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 9.5.1.1 of the protocol;
12. 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's choice group receivingLapatinib + Capacitabine. The ECGs should be submitted for central review;

Now reads as:

General note: in case assessments show abnormal results that warrant more extensive monitoring for safety, additional visits and assessments should be considered. For patients on physician's choice treatment in addition to the assessments in the flowchart guidance from the Summary of Product Characteristics/Prescribing Information of the specific treatments should be followed with regards to patient monitoring.

1. Following signing the "Study"-ICF an eligible patient should be randomized within 28 days. A "HER2 testing"-ICF may be used to assess the HER2 tumour status on archival tumour tissue to determine patient eligibility;
2. Day 1 assessments are to be done prior to study drug administration;

3. Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4. Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5. Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6. Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7. Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), urinary tests during treatment and at treatment discontinuation visit ~~in case of suspected pregnancy~~;
8. PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9. Immunogenicity samples will be taken in the SYD985 group only;
10. Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11. 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 9.5.1.1 of the protocol;
12. 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;

Section 5.2 patient population rationale (page 20)
Part II of the Phase I study is ongoing; expanded patient cohorts with specific cancer types, including late-line HER2-positive locally advanced or metastatic breast cancer, are being evaluated for safety and efficacy.

Now reads as:
Part II of the Phase I study is ongoing; expanded patient cohorts with specific cancer types, including 50 heavily pre-treated patients with late-line HER2-positive locally advanced or metastatic breast cancer, are being evaluated for safety and efficacy.

Section 5.5.1 SYD985 treatment (page 22)
Cardiac toxicity
Cardiac safety should be monitored in oncology patients commonly pre-treated with anthracycline therapy and/or treated with HER2-targeting agents. Transient, LVEF decreases have been observed in the Phase I study. LVEF decreases have also been observed in patients treated with trastuzumab and (ado-)trastuzumab emtansine and these often occur in the early treatment cycles[11-13]. Patients treated with these drugs are at increased risk of developing congestive heart failure or dysfunction, particularly following anthracycline therapy.
Cardiotoxicity is closely monitored in the study by performing LVEF and ECGs, and by measuring cardiac troponin regularly during SYD985 treatment. Patients with an increased risk of developing cardiac dysfunction, as defined in this protocol, are not eligible to participate in the study.

Now reads as:
Cardiac toxicity
Cardiac safety should be monitored in oncology patients commonly pre-treated with anthracycline therapy and/or treated with HER2-targeting agents. Transient, LVEF decreases have been observed in the Phase I study. LVEF decreases have also been observed in patients treated with trastuzumab and (ado-)trastuzumab emtansine and these often occur in the early treatment cycles[11-13]. Patients

treated with these drugs are at increased risk of developing congestive heart failure or dysfunction, particularly following anthracycline therapy.
Cardiotoxicity is closely monitored in the study by performing LVEF and ECGs, and by measuring cardiac troponin regularly during SYD985 treatment. Patients with an increased risk of developing cardiac dysfunction, as defined in this protocol, are not eligible to participate in the study. Any clinically relevant electrolyte disturbance (e.g. hypomagnesaemia and hypokalemia) should be corrected as appropriate.

Section 5.5.1 Physician's choice treatment (page 23) has been added
For safety considerations on the physician's choice treatments the information as described in the local Summary of Product Characteristics/Prescribing Information (SmPC/PI) of the specific treatments should be consulted. SYD985.002 is a global study and details may differ per country, therefore the investigator should consult the SmPC/PI as approved by their local country medicines agency (e.g. FDA, EMA, MHRA etc.). The local SmPC/PI will be provided and is to be filed in the ISF.

When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation, all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. If, for example, based on information in the medical history or the laboratory values of the patient one of the treatment options in the physician's choice group is contraindicated, that particular patient would have only three options of physician's choice treatment. Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.

During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

This protocol cannot address every safety consideration for all of the 'physician's choice' options. The investigator is referred to respective local summaries of product characteristics or prescribing information for specific guidance. In particular it is noted that there is variation among the options with regard to:

- duration of contraception after the last of study therapy administration;
- duration to avoid live vaccines before, during, and after study therapy administration;
- drug-drug interactions, in particular with regard to cytochrome P450 system.

Section 5.6 Benefit – Risk assessment (page 23) has been added
Based on the Phase I experience it can be concluded that there is a positive benefit/risk for patients with late-line HER2-positive locally advanced or metastatic breast cancer who have had progression

either during or after at least two HER2-targeting treatment regimens in the locally advanced or metastatic setting or after (ado-)trastuzumab emtansine treatment in the locally advanced or metastatic setting. Therefore SYD985 represents a reasonable treatment option for the intended patient population in this study.

Section 7 Study design (page 24)
The study will end when:

- All patients have completed the treatment discontinuation visit, or
- Sufficient survival follow-up information is obtained to enable analysis, or
- The trial is terminated by the Sponsor.

Now reads as:
The study will end when:

- All patients have completed the treatment discontinuation visit, or
- Sufficient survival follow-up information is obtained to enable analysis, or
- The trial is terminated by the Sponsor.

When the study is ended before all patients have discontinued study treatment, individual patients who benefit from SYD985 treatment will be enabled to receive further SYD985 treatment.

Section 8.1 Eligibility Criteria (page 24) following details have been added
When evaluating a patient for participation into the study the investigator should first consider which combination treatment would be prescribed if the patient would be randomized to the physician's choice group. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. Only after it is concluded that at least one of the four treatment options in the physician's choice group would be an appropriate way to treat the patient, the patient can be considered for the study as per inclusion/exclusion criteria.

Section 8.1.1 Inclusion Criteria (page 24)
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component are not eligible;

Now reads as:
5. Patients must have measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients with bone-only sclerotic disease without a lytic component, or patients who have bone-only metastases requiring endocrine therapy or patients with non-visceral metastases requiring endocrine therapy, are not eligible;

Section 9.4.2 Physician's choice treatment (page 29)
Physician's choice therapy options:

- Option 1: Lapatinib + Capecitabine
- Option 2: Trastuzumab + Capecitabine

- Option 3: Trastuzumab + Vinorelbine
- Option 4: Trastuzumab + Eribulin

The choice of reference therapy will be at the investigator's discretion and should be in accordance with local clinical practice.

For details on dosing and frequency the Summary of Product Characteristics of the prescribed drugs and local prescribing information should be used.

Now reads as:
Physician's choice therapy options:

- Option 1: Lapatinib + Capecitabine
- Option 2: Trastuzumab + Capecitabine
- Option 3: Trastuzumab + Vinorelbine
- Option 4: Trastuzumab + Eribulin

The choice of reference therapy will be at the investigator's discretion and should be in accordance with local clinical practice. During this evaluation all routine clinical considerations, including treatment specific restrictions/contraindications as per SmPC/PI for the physician's choice treatment options, should be taken into account. During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

~~For details on dosing and frequency the Summary of Product Characteristics of the prescribed drugs and local prescribing information should be used.~~

Section 9.5.2 Physician's choice treatment (page 31)
Dosing of physician's choice treatments can be modified (reduced, delayed) according to local clinical practice.

If one of the two agents of the combination regimen is discontinued the therapy can be continued with a single agent. However, if both agents of the regimen are discontinued for more than 42 days from the last dose the patient will be considered to have discontinued treatment.

Now reads as:
During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed. In particular with regards to:

- Contraindications, Warnings and precautions, Adverse events;
- Posology and method of administration, Dosage and administration;
- Interactions;
- Fertility, Special populations.

Dosing of physician's choice treatments can be modified (reduced, delayed) according to local clinical practice.

If one of the two agents of the combination regimen is discontinued the therapy can be continued with a single agent. However, if both agents of the regimen are discontinued for more than 42 days from the last dose the patient will be considered to have discontinued treatment.

Section 10 Pretreatment and concomitant medication and non-drug therapies (page 33)
Information on all prior received anticancer therapies must be recorded in the eCRF. Washout criteria apply for prior anticancer therapy as described in exclusion criterion 1. Other pre-treatment medication and concomitant medication used between 14 days prior to signing "Study"-ICF till the treatment discontinuation visit should be recorded in the eCRF. 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.

Patients are allowed to receive supportive care therapies concomitantly during the study. Patients who receive anthracycline treatment within 12 weeks prior to randomization are not allowed to participate in the study. No other chemotherapy, immunotherapy, or experimental medications are permitted from 4 weeks prior to randomization, radiation therapy from 2 weeks prior to randomization, and 1 week for hormone therapy, during study treatment and (if possible) up to 30 days after the last study treatment dose.

During study treatment and up to 30 days after the last treatment dose palliative radiotherapy is allowed only for the symptomatic treatment of painful bone lesions identified at baseline. Please contact the Medical Monitor for approval.

Patients who have disease control outside the brain, defined as having received clinical benefit (i.e. partial response (PR) or complete response (CR) of any duration, or stable disease (SD) for ≥ 4 months) but who have brain metastases that will benefit from treatment with radiation in the opinion of the investigator will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessment). Please contact the Medical Monitor for approval. Patients must not miss more than one 21-day cycle for the treatment of their brain disease to continue on therapy.

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 will be prescribed to patients in the SYD985 group, 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.

Patients of childbearing potential must use effective contraception during the study, and up to 6 months after last study drug dose. Acceptable forms of contraception include two of the following:

- Established use of oral, injected, implanted or other form of hormonal method of contraception;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Condom with spermicidal foam/gel/film/cream/suppository;
- Diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository.

The above contraception is not a requirement in the case of any of the following:

- Patient or sole partner of patient is surgically sterilized;
- True sexual abstinence.

Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable forms of contraception.

Now reads as:
Information on all prior received anticancer therapies must be recorded in the eCRF. Washout criteria apply for prior anticancer therapy as described in exclusion criterion 1. Other pre-treatment medication and concomitant medication used between 14 days prior to signing "Study"-ICF till the treatment discontinuation visit should be recorded in the eCRF. 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.

Patients are allowed to receive supportive care therapies concomitantly during the study. Patients who receive anthracycline treatment within 12 weeks prior to randomization are not allowed to participate in the study. No other chemotherapy, immunotherapy, or experimental medications are permitted from 4 weeks prior to randomization, radiation therapy from 2 weeks prior to randomization, and 1 week for hormone therapy, during study treatment and (if possible) up to 30 days after the last study treatment dose.

<u>During physician's choice treatment guidance from the SmPC/PI of the specific treatments should be followed with regards to co-medications that are contraindicated or are to be used with precaution.</u>

During study treatment and up to 30 days after the last treatment dose palliative radiotherapy is allowed only for the symptomatic treatment of painful bone lesions identified at baseline. Please contact the Medical Monitor for approval.

Patients who have disease control outside the brain, defined as having received clinical benefit (i.e. partial response (PR) or complete response (CR) of any duration, or stable disease (SD) for ≥ 4 months) but who have brain metastases that will benefit from treatment with radiation in the opinion of the investigator will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessment). Please contact the Medical Monitor for approval. Patients must not miss more than one 21-day cycle for the treatment of their brain disease to continue on therapy.

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 will be prescribed to patients in the SYD985 group, 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.

Patients of childbearing potential must use 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.[18]
Acceptable forms of contraception include two of the following:

- Established use of oral, injected, implanted or other form of hormonal method of contraception;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Condom with spermicidal foam/gel/film/cream/suppository;
- Diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository.

The above contraception is not a requirement in the case of any of the following:

- Patient or sole partner of patient is surgically sterilized;
- True sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient).

Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods), progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action, and withdrawal are not acceptable forms of contraception.

Section 11.9 Pregnancy test (page 37)
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening and urine pregnancy tests during treatment in case of suspected pregnancy will be performed at the local laboratory.

Now reads as:
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and urine pregnancy tests during treatment ~~in case of suspected pregnancy~~ on Day 1 of each cycle and at the treatment discontinuation visit will be performed at the local laboratory.

Section 11.16 ECG assessment (page 40)
Table 7: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration#
4	Day 1: Before study drug administration#
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)#
Every subsequent 4th cycle	Day 1: Before study drug administration#
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving Lapatinib + Capecitabine.
#For patients in physician's choice group receiving Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1 and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2hours) after the Cycle 4 Day 1 ECG.

Now reads as:
Table 8: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration#
3	Day 1: Before study drug administration#
4	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
Every subsequent 4th cycle	Day 1: Before study drug administration#
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine.
#For patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2 hours) after the Cycle 4 Day 1 ECG.

Section 16 References (page 67) a reference has been added

(18) Clinical trial Facilitation Group. Recommendations related to contraception and pregancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

Appendix 5 Protocol Amendment III

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment III (leading to Protocol Version 4.0)
Amendment Date:	11 September 2018
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared for the following reasons:

- Section 9.5.1 has been updated to add the possibility to reduce dosing to 0.6 mg/kg which has been shown to be an effective and safe dose in the phase I study.
- Section 11.9 and the flowchart have been updates to add the possibility for serum pregnancy test in addition to urine pregnancy test as routinely performed in several clinical sites.
- Section 12.10, 14.7 and the synopsis have been updated to describe that the DMC will assess the assumptions underlying the sample size estimation.
- Section 2 has been updated to reflect changes in the vendor responsibilities.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 4 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: Data Monitoring Committee (page 6)
No interim analysis will be performed. Safety will be monitored on an ongoing basis during the entire study by an independent external Data Monitoring Committee (DMC), of which the composition, roles and responsibilities will be described in a separate charter.

Now reads as:
~~No interim analysis will be performed.~~ Safety will be monitored on an ongoing basis during the entire study by an independent external Data Monitoring Committee (DMC), of which the composition, roles and responsibilities will be described in a separate charter. As part of their evaluation the DMC will assess if the assumptions underlying the sample size estimation with regards to drop-out rates are met, and may advise to change the planned sample size in case of serious departures.

Section 1.1 Study flowchart (page 9)

2. Day 1 assessments are to be done prior to study drug administration;
3. Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4. Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5. Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6. Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7. Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), urinary tests during treatment and at treatment discontinuation visit;
8. PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9. Immunogenicity samples will be taken in the SYD985 group only;
10. Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11. 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 9.5.1.1 of the protocol;
12. 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13. ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14. For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;

15. The tumour measurements should be submitted for central review;
16. Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17. Tumour evaluation at the treatment 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 visit;
18. Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19. During the survival follow-up only initiation of new anticancer medication should be documented.

Now reads as:

2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;
16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.

Section 2 (page 12)

Central Image Analysis:
(RECIST evaluation)

[redacted]

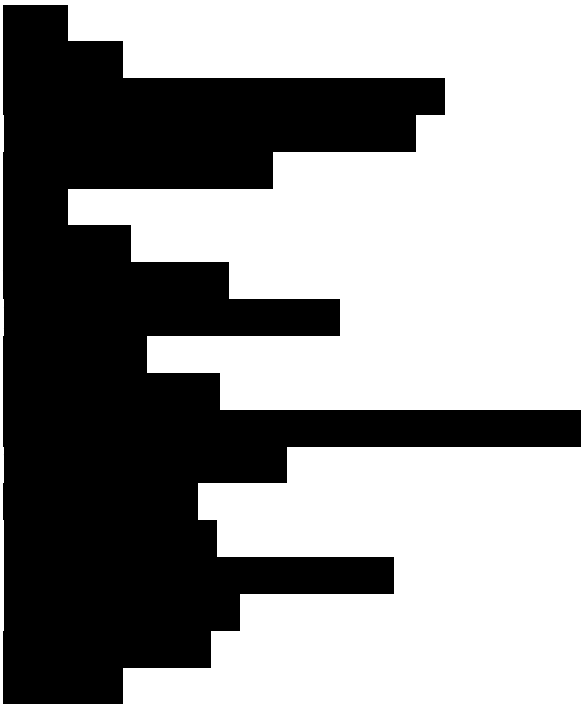
Central ECG Centre:
(ECG evaluation)

Central Laboratory:
(Safety laboratory & logistics)

Central Laboratory:
(for PK total SYD985, SYD985 DAR≥1 and immunogenicity)

Central Laboratory:
(for PK SYD986)

Central Laboratory:
(for HER2 Tumour expression)



Now reads as:

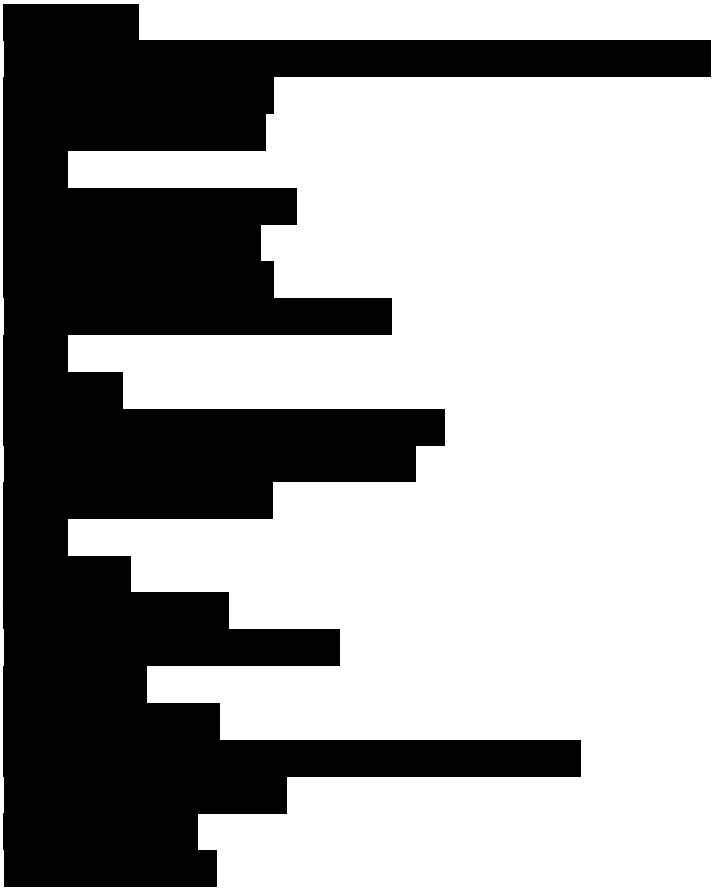
Central Image Analysis:
(RECIST evaluation)

Central ECG Centre:
(ECG evaluation)

Central Laboratory:
(Safety laboratory & logistics)

~~**Central Laboratory:**~~
~~**(for PK total SYD985, SYD985 DAR≥1 and immunogenicity)**~~

Central Laboratory:
(for PK SYD986, <u>total SYD985, SYD985 DAR≥1 and immunogenicity</u>)



Central Laboratory:
(for HER2 Tumour expression)

[redacted]

Central Laboratory:
(Neutralizing antibody assay)

Section 9.4.1 (page 30)
SYD985 1.2 mg/kg will be administered every three weeks (± 1 day) by intravenous infusion.

Now reads as:
SYD985 1.2 mg/kg will be administered every three weeks (± ~~1~~3 day) by intravenous infusion.

Section 9.5.1 (page 32)
Dose delays for SYD985-related toxicities, other than the ones specified below, should be handeled 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 will be discontinued from study treatment and will be followed for survival follow-up as described in Section 11.22.

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 discontinued from treatment. Dose escalation is not allowed after a dose reduction.

As indicated in Section 9.4.1 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 interruption of infusion will be discontinued from study treatment.

Protocol requirements for specific toxicities are outlined below.

Now reads as:

Dose delays for SYD985-related toxicities, other than the ones specified below, should be ~~handeled~~ 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 will be discontinued from study treatment and will be followed for survival follow-up as described in Section 11.22.

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.

As indicated in Section 9.4.1 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 interruption of infusion will be discontinued from study treatment.

Protocol requirements for specific toxicities are outlined below.

Section 11.9 (page 40)
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and urine pregnancy tests during treatment on Day 1 of each cycle and at the treatment discontinuation visit will be performed at the local laboratory.

Women of childbearing potential participating in this clinical study should be instructed to use adequate contraceptive barriers to prevent them from getting pregnant while using study drug (see also Section 10).

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.

Now reads as:
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and serum or urine pregnancy tests during treatment on Day 1 of each cycle and at the treatment discontinuation visit will be performed at the local laboratory.

Women of childbearing potential participating in this clinical study should be instructed to use adequate contraceptive barriers to prevent them from getting pregnant while using study drug (see also Section 10).

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.

Section 11.16 (page 43)

Table 9: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration[#]
3	Day 1: Before study drug administration[#]
4	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
Every subsequent 4th cycle	Day 1: Before study drug administration[#]
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine.

[#]For patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2 hours) after the Cycle 4 Day 1 ECG.

Now reads as:

Table 10: ECG assessment schedule

Cycle	**Time point**
Screening	Screening
1	Day 1: Before study drug administration
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
2	Day 1: Before study drug administration[#]
3	Day 1: Before study drug administration[#]
4	Day 1: Before study drug administration[#]
	Day 1: 30 minutes after end of infusion (±10 minutes)*
	Day 2: 24 hours after study drug administration (±2 hours)
Every subsequent 4th cycle	Day 1: Before study drug administration[#]
Treatment discontinuation	Treatment discontinuation

*not applicable for patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine.

[#]For patients in physician's choice group receiving the oral treatment combination Lapatinib + Capecitabine the timing of the ECG on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1 does not have to be correlated to the study drug administration. The ECG on Cycle 4 Day 2 should be 24 hours (± 2 hours) after the Cycle 4 Day 1 ECG.

Section 12.10 (page 52)
Details on the responsibilities, activities and deliverables of the external Data Monitoring Committee (DMC) are detailed in a separate charter.

Now reads as:
Details on the responsibilities, activities and deliverables of the external Data Monitoring Committee (DMC) are detailed in a separate charter. As part of their evaluation the DMC will assess if the assumptions underlying the sample size estimation with regards to drop-out rates are met, and may advise to change the planned sample size in case of serious departures.

Section 14.5.3.1 (page 59)
Time to response is the time between the date of randomization until first documented response (CR or PR) according to RECIST 1.1. All patients will be included in time to response calculations. Patients who did not achieve a confirmed CR or PR will be censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed of death due to any cause) or at the date of last adequate tumour assessment date otherwise.
Time to response will be analyzed based on the data observed in the FAS population and will be determined primarily by independent central review of tumour assessment (an analysis based on investigator tumour assessment will also be performed). Time to response will be summarized for the two treatment groups using descriptive statistics.

Now reads as:
Time to response is the time between the date of randomization until first documented response (CR or PR) according to RECIST 1.1. All patients will be included in time to response calculations. Patients who did not achieve a ~~confirmed~~ CR or PR will be censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed of death due to any cause) or at the date of last adequate tumour assessment date otherwise.
Time to response will be analyzed based on the data observed in the FAS population and will be determined primarily by independent central review of tumour assessment (an analysis based on investigator tumour assessment will also be performed). Time to response will be summarized for the two treatment groups using descriptive statistics.

Section 14.7 (page 62)
The primary efficacy endpoint of this study is PFS based on independent central review of tumour assessment. The primary efficacy analysis will be event driven.

In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 20% drop out in the physician's choice group

and 30% in the SYD985 group, a minimal number of 309 patients is required. To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients. Allocation is 2:1 resulting in 230 to be allocated to the SYD985 group and 115 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

Now reads as:
The primary efficacy endpoint of this study is PFS based on independent central review of tumour assessment. The primary efficacy analysis will be event driven.

In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 20% drop out in the physician's choice group and 30% in the SYD985 group, a minimal number of 309 patients is required. To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients. Allocation is 2:1 resulting in 230 to be allocated to the SYD985 group and 115 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

No formal interim analysis will be performed. As part of their evaluation the DMC will assess if the assumptions underlying the sample size estimation with regards to drop-out rate are met, and may advise to change the planned sample size in case of serious departures. Such sample size re-estimation will not be considered a formal interim analysis as no between-group comparison of event-rates will be performed. Therefore, the primary analysis will be performed at the set 5% significance level.

Appendix 2 Tumour evaluation criteria (page 75)
Target lesions should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). In cases where the radiologist are not comfortable assigning a measurement to a very small lesions, the lesions should either be recorded as likely disappears (I.e. 0 mm) or 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). 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.

Now reads as:

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 ~~, even when very small (e.g. 2 mm). In cases where the radiologist are not comfortable assigning a measurement to a very small lesions, the lesions should either be recorded as likely disappears (I.e. 0 mm)~~ 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.

Appendix 6 Protocol Amendment IV

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment IV (leading to Protocol Version 5.0)
Amendment Date:	12 April 2019
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared for the following reasons:

- Upon request of the DMC Keratitis grade ≥2 has been added as an adverse event of special interest
- In consultation with the Steering committee and the DMC Section 8.2 has been updated to add the possibility to allow re-screening for patients for whom during screening on the brain CT/MRI a previously unknown asymptomatic metastasis is observed.
- Section 11.9 and the flowchart have been updated to add the possibility to perform the pregnancy test up to 3 days before Day 1 of a new cycle for practical reasons.
- Section 11.21 and the flowchart have been updated to add that the treatment discontinuation visit should be performed before new anti-cancer treatment is initiated.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 5 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: Sample size (page 6)
Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

Now reads as:
Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (~~2/>2~~ 1 or 2/more than 2), and prior treatment with pertuzumab (yes/no) as stratification factors.

Study flowchart (page 9)
2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;

14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;
16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.

Now reads as:

2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment (should be done on Day1 of the new cycle, but may be done up to 3 days before) and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;
16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.
20 The end of treatment visit needs to be performed 28-42 days after the last dose of study drug or before new anticancer treatment is initiated, whichever comes first.

Section 8.2 (page 28)

Patients who signed the "HER2 testing" and/or "Study"-ICF but subsequently failed to meet the inclusion and/or exclusion criteria are defined as 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. If a patient has clinically significant deviations in laboratory values as mentioned in inclusion criterion 8 and/or exclusion criterion 6 and/or clinically significant

deviations in LVEF as detailed in exclusion criterion 5, it is not allowed to repeat the laboratory assessment and the patient cannot be randomized.

The only exception is re-screening for HER2 status. If the result was HER2-negative based on archived material the site could consider sending fresh material to reassess the HER2 status.

Now reads as:
Patients who signed the "HER2 testing" and/or "Study"-ICF but subsequently failed to meet the inclusion and/or exclusion criteria are defined as 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. If a patient has clinically significant deviations in laboratory values as mentioned in inclusion criterion 8 and/or exclusion criterion 6 and/or clinically significant deviations in LVEF as detailed in exclusion criterion 5, it is not allowed to repeat the laboratory assessment and the patient cannot be randomized.

The only two exceptions ~~is re-screening for HER2 status~~ are:

- If the result was HER2-negative based on archived material the site could consider sending fresh material to reassess the HER2 status.
- Patients for whom during screening on the brain CT/MRI a previously unknown asymptomatic metastasis is observed. These patients can be candidates for re-screening when the following conditions apply: (1) The treatment for brain metastases should be finalized more than 8 weeks prior to start re-screening; (2) There should be evidence of disease stability; (3) Enrolment for the SYD985.002 study should still be open. Please contact the medical monitor for approval. Note that for these patients all screening procedures should be repeated, excluding the central HER2-testing and the whole body bone scan if the previous scan showed no bone metastasis and there is no clinical suspicion of newly developed metastatic bone lesion(s).

Section 9.1 (page 29)
Using a computer-generated randomization list, eligible patients will be randomly assigned in a 2:1 ratio to receive SYD985 or Physician's choice therapy. The allocation will be stratified for geographical region (Europe and Singapore, North America), the number of prior treatment lines for advanced breast cancer (excluding hormone therapy) (2, more than 2), and prior treatment with pertuzumab (yes, no).

Now reads as:
Using a computer-generated randomization list, eligible patients will be randomly assigned in a 2:1 ratio to receive SYD985 or Physician's choice therapy. The allocation will be stratified for geographical region (Europe and Singapore, North America), the number of prior treatment lines for advanced breast cancer (excluding hormone therapy) (1 or 2, more than 2), and prior treatment with pertuzumab (yes, no).

Section 9.5.1.4 (page 33)
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, the 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. 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.

Now reads as:
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, the tumour evaluation CT scans should be carefully evaluated for lung changes e.g. by means of high resolution CT. Infectious and metastatic disease-related aetiologies should be ruled out. Patients should be advised to promptly report any new or worsening respiratory symptoms. 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.

Section 11.9 (page 40)
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and serum or urine pregnancy tests during treatment on Day 1 of each cycle and at the treatment discontinuation visit will be performed at the local laboratory.

Now reads as:
To exclude pregnancy in women of childbearing potential, a serum pregnancy test at screening (between day -10 and day -1) and serum or urine pregnancy tests during treatment on Day 1 of each cycle (may be done up to 3 days before) and at the treatment discontinuation visit will be performed at the local laboratory.

Section 11.21 (page 45)
The treatment discontinuation visit should occur 4-6 weeks (28-42 days) after the last administration of study drug (SYD985, trastuzumab, vinorelbine, eribulin, lapatinib, or capecitabine, whichever is discontinued last).

Now reads as:
The treatment discontinuation visit should occur 4-6 weeks (28-42 days) after the last administration of study drug (SYD985, trastuzumab, vinorelbine, eribulin, lapatinib, or capecitabine, whichever is discontinued last) or before new anticancer treatment is initiated, whichever comes first.

Section 12.1 (page 47)

Protocol defined events of special interest	The following events are adverse events of special interest (AESIs) and will need to be reported to the CRO expeditiously, irrespective of regulatory seriousness criteria or causality: • Pneumonitis, • Severe eye toxicity grade ≥ 3, • LVEF decrease to < 50%.

Now reads as:

Protocol defined events of special interest	The following events are adverse events of special interest (AESIs) and will need to be reported to the CRO expeditiously, irrespective of regulatory seriousness criteria or causality: • Pneumonitis, • Severe eye toxicity grade ≥ 3, • Keratitis grade ≥ 2, • LVEF decrease to < 50%.

Section 12.3.1 (page 48)
The investigator will determine the severity of AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03 or higher). AEs that are not listed in the CTCAE should be graded according to Table 4.

Now reads as:
The investigator will determine the severity of AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03 ~~or higher~~). AEs that are not listed in the CTCAE should be graded according to Table 4.

Section 12.5 (page 54)
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 most recent version of Company Core Safety Information as appended to the the Investigator's Brochure is to be used to assess the expectedness of an AE for SYD985. The reference Summary of product characteristics is to be used to assess expectedness for Physician's choice treatments.
Investigators must report all SAEs to their Independent Ethic Committee (IEC)/ Institutional Review Board (IRB) responsible for the study. In addition, in case of a SUSAR occurring in a patient treated with Physician's Choice treatment the investigator is responsible for reporting the SUSAR to the respective manufacturer.

Now reads as:
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 most recent version of Company Core Safety Information as appended to the~~ section 6.8 of the Investigator's Brochure contains the reference safety information and is to be used to assess the expectedness of an AE for SYD985. The reference Summary of product characteristics is to be used to assess expectedness for Physician's choice treatments.
Investigators must report all SAEs to their Independent Ethic Committee (IEC)/ Institutional Review Board (IRB) responsible for the study. In addition, in case of a SUSAR occurring in a patient treated with Physician's Choice treatment the investigator is responsible for reporting the SUSAR to the respective manufacturer.

Section 12.6 (page 54)
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:

- Pneumonitis;
- Severe eye toxicity grade ≥ 3;
- LVEF decrease to < 50%.

Now reads as:
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:

- Pneumonitis;
- Severe eye toxicity grade ≥ 3;
- Keratitis grade ≥ 2;
- LVEF decrease to < 50%.

Appendix 7 Protocol Amendment V

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment V (leading to Protocol Version 6.0)
Amendment Date:	24 May 2019
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared upon request of the regulatory authorities. The changes are summarized below:

- Section 5.5.1 has been updated to include additional information on ILD/Pneumonitis.
- Section 9.5.1.4 dose modifications for ILD/pneumonitis have been elaborated.
- Section 11.5 oxygen saturation by pulse oximetry has been added to the vital signs assessments at all visits.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 6 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: Planned clinical study period (page 6)
First patient first visit: Q3 2017
Last patient first visit: Q2 2019
Last patient last visit: H1 2019

Now reads as:
First patient first visit: Q3 2017
Last patient first visit: ~~Q2 2019~~ H2 2019
Last patient last visit: ~~H1 2019~~ H2 2020

Study flowchart (page 9)
2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment (should be done on Day1 of the new cycle, but may be done up to 3 days before) and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;

16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.
20 The end of treatment visit needs to be performed 28-42 days after the last dose of study drug or before new anticancer treatment is initiated, whichever comes first.

Now reads as:

2 Day 1 assessments are to be done prior to study drug administration;
3 Weight should be measured before the start of a new cycle, this may be done up to 7 days before the Day 1 visit;
4 Archived tumour material should be submitted for central analysis of HER2 status before randomization, this can be done after signing the "HER2 testing"-ICF. If there is no archival tumour material available a biopsy should be performed to obtain tumour material, this can only be done after signing the "Study"-ICF. The HER2 tumour status will be assessed by a central laboratory using IHC and ISH;
5 Blood sampling for haematology/chemistry, cardiac troponin, and urinalysis should be done as closely as possible to the start of the new cycle, but may be done up to 3 days before. Analyses should be performed at a local laboratory. Results of the local laboratory should be available before the start of the new cycle to determine whether the patient can continue. 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. Analyses for haematology/chemistry, and cardiac troponin should also be performed at the central laboratory;
6 Either cardiac troponin I or T (using a high sensitivity assay) can be measured as long as the same assay is used throughout the study for an individual patient;
7 Pregnancy test in women of childbearing potential: serum test at screening (between day -10 and day -1), serum or urinary tests during treatment (should be done on Day1 of the new cycle, but may be done up to 3 days before) and at treatment discontinuation visit;
8 PK samples will be taken in the SYD985 treatment group only. See for details the PK sampling scheme on page 10;
9 Immunogenicity samples will be taken in the SYD985 group only;
10 Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as LVEF assessment 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;
11 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 9.5.1.1 of the protocol;
12 12-lead ECGs should be recorded in triplicate. ECGs should be obtained before study drug administration for all patients. In addition ECGs should be obtained 30 minutes after the end of infusion at the day of first study drug administration in cycle 1 and cycle 4 in all patients excluding the patients in the Physician's Choice group receiving the oral treatment combination lapatinib + capacitabine. The ECGs should be submitted for central review;
13 ECG should be obtained 24 hours (± 2 hours) after study drug administration. The ECGs should be submitted for central review;
14 For tumour measurements, a CT or MRI scan should be performed every 6 weeks (± 3 days) after the date of randomization for the first 42 weeks and every 9 weeks (± 3 days) thereafter, independent of dosing delays. The methodology and imaging levels should remain the same at baseline and subsequent evaluations for a given patient;
15 The tumour measurements should be submitted for central review;
16 Administration of SYD985 or administration of physician's choice in a 21-days (3 weeks) regimen (± 3 days) until disease progression or unacceptable toxicity. For SYD985 no recalculation of the 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;
17 Tumour evaluation at the treatment 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 visit;
18 Patients should be followed up until death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first;
19 During the survival follow-up only initiation of new anticancer medication should be documented.
20 The end of treatment visit needs to be performed 28-42 days after the last dose of study drug or before new anticancer treatment is initiated, whichever comes first.
21 Vital signs include blood pressure, heart rate, body temperature, and oxygen saturation by pulse oximetry.

Section 2 (page 11)
CRO
(clinical services)

[redacted]

Now reads as:
CRO
(clinical services)

[redacted]

Section 5.5.1 (page 22)
Pneumonitis
Pneumonitis was reported in the Phase I study. Pneumonitis and lung consolidations are also reported for other anticancer drugs, including anti-PD1 antibodies[8;9], everolimus (mTOR inhibitor), and the anti-HER2 agents lapatinib and (ado-)trastuzumab emtansine[10].
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 pulmonary toxicity in an early stage, the tumour evaluation CT scans, which are initially done every 6 weeks, should be carefully evaluated for lung changes e.g. by means of high resolution CT. Patients should be advised to promptly report any new or worsening respiratory symptoms.

Now reads as:
Interstitial Lung Disease ILD/Pneumonitis
ILD/Pneumonitis was reported in the Phase I study. ILD/Pneumonitis and lung consolidations are also reported for other anticancer drugs, including anti-PD1 antibodies[8;9], everolimus (mTOR inhibitor), and the anti-HER2 agents lapatinib and (ado-)trastuzumab emtansine[10].
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 IDL/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug-induced ILD/pneumonitis. ILD/pneumonitis evaluation (regardless of stage) should always include a pulmonary consult, a high resolution CT, pulmonary function testing (PFTs), pulse oximetry and arterial blood gases (ABGs).
To detect pulmonary toxicity in an early stage, the tumour evaluation CT scans, which are initially done every 6 weeks, should be carefully evaluated for lung changes e.g. by means of high resolution CT. Patients should be advised to promptly report any new or worsening respiratory symptoms.

Section 9.5.1.4 (page 34)
SYD985 - Dose modifications for pneumonitis

Patients who experience Grade 3 or 4 pneumonitis will be discontinued from treatment. For patients who experience Grade 2 pneumonitis dosing must be delayed for up to 42 days from the last received dose. When the pneumonitis resolves to Grade 1 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 pneumonitis persists. The pneumonitis should be monitored for recovery.

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, the tumour evaluation CT scans should be carefully evaluated for lung changes e.g. by means of high resolution CT. Infectious and metastatic disease-related aetiologies should be ruled out. Patients should be advised to promptly report any new or worsening respiratory symptoms. 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.

Now reads as:
SYD985 - Dose modifications for ILD/pneumonitis

Patients who experience Grade 2, 3 or 4 ILD/pneumonitis will be discontinued from treatment. For patients who experience Grade ~~2~~ 1 ILD/pneumonitis dosing must be delayed for up to 42 days from the last received dose. When the ILD/pneumonitis resolves to Grade ~~1 or lower~~ 0 patients may continue treatment and a dose reduction should be considered. ~~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 pneumonitis persists.~~ Reversibility or stabilisation of ~~The~~ 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 IDL/pneumonitis are exploratory and they should not be used for diagnosis or monitoring of drug-induced ILD/pneumonitis. ILD/pneumonitis evaluation (regardless of stage) should always include a pulmonary consult, a high resolution CT, PFTs, pulse oximetry and ABGs.
To detect ILD/pneumonitis or other pulmonary toxicity in an early stage, the tumour evaluation CT scans should be carefully evaluated for lung changes e.g. by means of high resolution CT. Infectious and metastatic disease-related aetiologies should be ruled out. Patients should be advised to promptly report any new or worsening respiratory symptoms. 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.

Section 11.5 (page 38)
Vital signs assessments include blood pressure, heart rate, and body temperature. Vital signs should be measured at screening and at the time points as indicated in the flowchart (see Section 1.1). On Day1 of each cycle vital signs should be recorded before study drug administration.

Now reads as:
Vital signs assessments include blood pressure, heart rate, ~~and~~ body temperature, and oxygen saturation by pulse oximetry. Vital signs should be measured at screening and at the time points as indicated in the flowchart (see Section 1.1). On Day1 of each cycle vital signs should be recorded before study drug administration.

Section 12.5 (page 50)
The occurrence of any SAEs from signing of the "Study"-ICF up to the treatment 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 by telephone, fax or email. The notification must include a completed SAE form. The contact details of the [redacted] Pharmacovigilance Department are:

Pharmacovigilance Department [redacted]
Address: [redacted]
Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [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 in the form of a follow-up report 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 CRF and to the [redacted] Pharmacovigilance Department.

Now reads as:
The occurrence of any SAEs from signing of the "Study"-ICF up to the treatment 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 by telephone, fax or email. The notification must include a completed SAE form. The contact details of the [redacted] Pharmacovigilance Department are:

Pharmacovigilance Department [redacted]
Address: [redacted]
Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [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 in the form of a follow-up report 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 CRF and to the [redacted] Pharmacovigilance Department.

Section 12.6 (page 50)
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:

- Pneumonitis;
- Severe eye toxicity grade ≥ 3;

- Keratitis grade ≥ 2;
- LVEF decrease to < 50%.

All AESIs must be documented on an SAE Reporting Form and the same details need to be reported.

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.

The occurrence of any AESIs, from signing of the "Study"-ICF up to the treatment discontinuation visit (regardless of relationship to study drug) has to be notified (within 5 days of the investigator or designee becoming aware of the event) to the CRO by telephone, fax or email. The notification must include a completed SAE form. If a SAE occurs in conjunction with the AESI, then the reporting time frame for an SAE (24 hours) must be met.

The contact details of the [redacted] Pharmacovigilance Department are:
Address: [redacted]
Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [redacted]

The investigator or designee must report (within 5 days of becoming aware of the event) clinically significant follow-up information pertaining to the AESI in the form of a follow-up report 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 AESI has to be reported in the CRF and to the [redacted] Pharmacovigilance Department.

Now reads as:
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;
- Severe eye toxicity grade ≥ 3;
- Keratitis grade ≥ 2;
- LVEF decrease to < 50%.

All AESIs must be documented on an SAE Reporting Form and the same details need to be reported.

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.

The occurrence of any AESIs, from signing of the "Study"-ICF up to the treatment discontinuation visit (regardless of relationship to study drug) has to be notified (within 5 days of the investigator or designee becoming aware of the event) to the CRO by telephone, fax or email. The notification must

include a completed SAE form. If a SAE occurs in conjunction with the AESI, then the reporting time frame for an SAE (24 hours) must be met.

The contact details of the [redacted] Pharmacovigilance Department are:
Address: [redacted]
Fax: [redacted] or to the dedicated fax number indicated on the SAE Reporting Form
Email: [redacted]

The investigator or designee must report (within 5 days of becoming aware of the event) clinically significant follow-up information pertaining to the AESI in the form of a follow-up report 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 AESI has to be reported in the CRF and to the [redacted] Pharmacovigilance Department.

Section 13.1 (page 53)
The investigator should discontinue a patient from study treatment for reasons including but not limited to the following:

- Progressive disease;
- Unacceptable toxicity, including:
  - Clinically significant symptomatic cardiac disease (see Section 9.5.1.1);
  - 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 3 or 4 pneumonitis;
- Pregnancy;
- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest.

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

- Progressive disease;
- Unacceptable toxicity, including:
  - Clinically significant symptomatic cardiac disease (see Section 9.5.1.1);
  - 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 IDL/pneumonitis;
- Pregnancy;

- Substantial non-compliance with the requirements of the study;
- Investigator decision based on the patient's best interest.

Appendix 8 Protocol Amendment VI

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment VI (leading to Protocol Version 7.0)
Amendment Date:	22 October 2019
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared for the following reason:

- As part of their evaluation the independent DMC assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 7 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis: sample size (page 6)
In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 20% drop out in the physician's choice group and 30% in the SYD985 group, a minimal number of 309 patients is required. To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients. Allocation is 2:1 resulting in 230 to be allocated to the SYD985 group and 115 to the physician's choice group.

Now reads as:
In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of ~~20~~ 30% drop out in the physician's choice group and ~~30~~ 40% in the SYD985 group, a minimal number of ~~309~~ 423 patients is required. ~~To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients.~~ Allocation is 2:1 resulting in ~~230~~ 282 to be allocated to the SYD985 group and ~~115~~ 141 to the physician's choice group.

Protocol synopsis: Data Monitoring Committee (page 6)
Safety will be monitored on an ongoing basis during the entire study by an independent external Data Monitoring Committee (DMC), of which the composition, roles and responsibilities will be described in a separate charter. As part of their evaluation the DMC will assess if the assumptions underlying the sample size estimation with regards to drop-out rates are met, and may advise to change the planned sample size in case of serious departures.

Now reads as:
Safety will be monitored on an ongoing basis during the entire study by an independent external Data Monitoring Committee (DMC), of which the composition, roles and responsibilities will be described in a separate charter. As part of their evaluation the DMC ~~will assess if the~~ assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates ~~are met, and may advise to change the planned sample size in case of serious departures.~~. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis.

Section 12.10 (page 52)
Details on the responsibilities, activities and deliverables of the external Data Monitoring Committee (DMC) are detailed in a separate charter. As part of their evaluation the DMC will assess if the

assumptions underlying the sample size estimation with regards to drop-out rates are met, and may advise to change the planned sample size in case of serious departures.

Now reads as:
Details on the responsibilities, activities and deliverables of the external Data Monitoring Committee (DMC) are detailed in a separate charter. As part of their evaluation the DMC ~~will assess if the~~ assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates ~~are met, and may advise to change the planned sample size in case of serious departures.~~. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis.

Section 14.7 (page 62)
In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of 20% drop out in the physician's choice group and 30% in the SYD985 group, a minimal number of 309 patients is required. To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients. Allocation is 2:1 resulting in 230 to be allocated to the SYD985 group and 115 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

No formal interim analysis will be performed. As part of their evaluation the DMC will assess if the assumptions underlying the sample size estimation with regards to drop-out rate are met, and may advise to change the planned sample size in case of serious departures. Such sample size re-estimation will not be considered a formal interim analysis as no between-group comparison of event-rates will be performed. Therefore, the primary analysis will be performed at the set 5% significance level. Details of methods used will be provided in a separate analysis plan.

Now reads as:
In order to be able to detect a hazard ratio of 0.65 in PFS using the log-rank test, at 90% power, using a two-sided test at a significance level of $p < 0.05$, a total of 256 events are required. Assuming a 9 month recruitment period and 10 month follow up period, a median time to progression of 4.1 months for the physician's choice and assuming an average of ~~20~~ 30% drop out in the physician's choice group and ~~30~~ 40% in the SYD985 group, a minimal number of ~~309~~ 423 patients is required. ~~To adjust for departures from the assumptions (clinical and statistical) enrolment is targeted for at least 345 patients.~~ Allocation is 2:1 resulting in ~~230~~ 282 to be allocated to the SYD985 group and ~~115~~ 141 to the physician's choice group.

Randomization will be done by a permutated block design with a fixed block size, using world region (Europe and Singapore/North-America), the number of prior treatment lines for locally advanced or

metastatic breast cancer (excluding hormone therapy) (2/>2), and prior treatment with pertuzumab (yes/no) as stratification factors.

No formal interim analysis will be performed. As part of their evaluation the DMC ~~will assess if the~~ assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rate ~~are met, and may advise to change the planned sample size in case of serious departures~~. Such sample size re-estimation will not be considered a formal interim analysis as no between-group comparison of event-rates will be performed. Therefore, the primary analysis will be performed at the set 5% significance level. Details of methods used will be provided in a separate analysis plan.

Appendix 9 Protocol Amendment VII

CLINICAL STUDY PROTOCOL AMENDMENT

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

Abbreviated title:	TULIP
Protocol Number:	SYD985.002
Development phase:	Phase III
Drug product code:	SYD985
Drug substance:	Trastuzumab vc-seco-DUBA
EudraCT Number:	2017-001994-18
IND Number:	131333
Amendment:	Protocol Amendment VII (leading to Protocol Version 8.0)
Amendment Date:	18 January 2021
Authors Byondis BV:	[redacted]

Justification for the amendment
This substantial amendment has been prepared for the following reason:

- To include the possibility to analyse the primary endpoint of the trial when at least 95% of the patients have discontinued treatment.
- Section 2 has been updated to reflect changes in the vendor responsibilities.

Apart from editorial changes, version changes to the title page and table of contents, this has led to the following changes in the protocol text (all included in version 8 of the protocol). New text is underlined, deleted text is ~~strikethrough~~:

Protocol synopsis (efficacy analysis (page 5):
The primary PFS analysis will be performed when at least 256 PFS events have occurred and only after all patients have been enrolled.

Now reads as:
The primary PFS analysis will be performed when at least 256 PFS events have occurred, or when at least 95% of patients have discontinued treatment, and only after all patients have been enrolled.

Section 14.5.1.1 (page 57):
The primary PFS analysis will be performed when at least 256 PFS events have occurred, as assessed by central review, or when at least 95% of patients have discontinued treatment, and only after all patients have been enrolled.

Now reads as:
The primary PFS analysis will be performed when at least 256 PFS events have occurred, as assessed by central review, or when at least 95% of patients have discontinued treatment, and only after all patients have been enrolled.

Section 2 (page 12):

Central Laboratory:
(Neutralizing antibody assay)

[redacted]

Now reads as:
~~**Central Laboratory:**~~
~~**(Neutralizing antibody assay)**~~

[redacted]