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.

NCT03262935

Version 3.0, dated 29 April 2021

Statistical Analysis Plan for Interventional Studies
Text and TFL Shells

SAP Text Version Number: 3.0
SAP Text Date: 29-Apr-2021

Sponsor Name: Byondis BV

Protocol Number: 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 unrespectable locally advanced or metastatic breast cancer.

Protocol Version and Date:
Protocol 1 May-2017
Protocol 2 25-Aug-2017
Protocol 3 09-Nov-2017
Protocol 4 11-Sep-2018
Protocol 5 12-Apr-2019
Protocol 6 25-May-2019
Protocol 7 22-Oct-2019
Protocol 8 18-Jan-2021

██████████ **Project Code:** ███████

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Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	12-Apr-2018	▮▮▮▮▮▮▮▮	Initial Release Version
2.0	20-Jan-2021	▮▮▮▮▮▮▮▮	Include protocol amendments, COVID-19, top three eye disorders and ▮▮▮▮▮▮ lung review
3.0	30-Apr-2021	▮▮▮▮▮▮▮▮	Clarify that visit windowing is used for the safety repeated measures, delete demographics table pre vs. during COVID for the FAS, indicate combining strata will be considered, clarify inferential analysis model for proportional hazards.

I confirm that I have reviewed this document and agree with the content.

Approvals		
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1.   Glossary of Abbreviations

Abbreviation	Description
ADA	Anti-Drug Antibody
ADaM	Analysis Dataset Model
ADaMIG	Analysis Dataset Model Implementation Guidelines
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	ALanine aminoTransferase
AP	Alkaline phosphatase
AST	ASpartate aminoTransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-Time Curve
BLQ	Below Level of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C	Cycle
CDISC	Clinical Data Interchange Standards Consortium
CBR	Clinical Benefit Rate
CI	Confidence Interval
CK	Creatine Kinase
CL	Plasma Clearance
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Concentration for the Dose Interval
CR	Complete Response
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CV	Coefficient of Variation
D	Day
DMC	Data Monitoring Committee
DNA	Deoxyribose Nucleic Acid
DOR	Duration of Response
DRM	Data Review Meeting

Abbreviation	Description
ECD	Extracellular Domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOI	End of Infusion
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow Up
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
HDL	High Density Lipoprotein
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
HRr	Hormone Receptor
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICR	Independent Central Review
IEC	Independent Ethics Committee
ITT	Intent-to-Treat
IV	Intravenously
λ_z	Terminal Elimination Rate Constant
LDL	Low Density Lipoprotein
LS	Least squares
LVEF	Left Ventricular Ejection Fraction
Max	Maximum
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model Repeated Measurement
MUGA	Multigated Acquisition
N/A	Not Applicable
NCI	National Cancer Institute
NE	Not Evaluable

Abbreviation	Description
ORR	Objective Response Rate
OS	Overall Survival
PCI	Potential Clinical Importance
PD	Pharmacodynamics
PDS	Pharmacodynamics Set
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PPS	Per-Protocol Set
PR	Partial Response
PT	Preferred Term
QC	Quality Control
QoL	Quality of life
RBC	Red Blood cell Count
RECIST	Response Evaluation Criteria for Solid Tumours
SACT	Subsequent Anti-cancer Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Screened Set
SYD985	Trastuzumab vc-*seco*-DUBA
SYD986	DUocarmycin hydroxyBenzamide Azaindole (DUBA, active toxin)
$t_{1/2}$	Terminal Elimination Half-life
TEAE	Treatment Emergent Adverse Event
TFBUP	Tear Film Break Up Time
TLF	Table, Listing and Figure
T_{max}	Time to C_{max}
T_{min}	Time of C_{min}
TTR	Time to Response
ULN	Upper Limit of Normal
V	Volume of Distribution

Abbreviation	Description
WBC	White Blood cell
WHO	World Health Organization

2.   Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1.   Responsibilities

████████████ is responsible for the production and quality control of the baseline, efficacy, pharmacokinetic (PK), safety and quality of life (QoL) tables, listings and figures (TLFs) and will perform the statistical analyses for these.

In addition to the current SAP, additional SAP(s) will be prepared to analyse immunogenicity, electrocardiogram (ECG) data and exploratory correlation analysis (e.g. exposure/response and exposure/safety). These analyses will not be performed by ████████████ but be carried out by Byondis and/or other parties to which Byondis has delegated this responsibility. The results of these analyses will be reported separately.

Listings will be provided by ████████████ for ECG data and immunogenicity data as collected on the Case Report Form (CRF).

For samples collected but not yet analysed (e.g. circulating tumour (ct) DNA and human epidermal growth factor receptor (HER) 2 – extracellular domain (ECD)) listings of sample dates and times will be provided.

2.2.   Timings of Analyses

Analysis of the Primary Endpoint: Progression free survival (PFS) analysis will be performed when at least 256 PFS events have occurred, as assessed by central review, or at least 95% of patients have discontinued treatment and only after all patients have been enrolled. All TLFs and analysis will be completed at this time. An interim assessment of overall survival (OS) will be performed at this time with no implications in terms of future study conduct.

Survival Follow Up: The final analysis is planned after the study is ended. 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.

All TLFs and analysis, including PFS, will be completed at this time. Unless otherwise specified, the analysis includes all data collected in the database through to the time of the database lock.

Data Monitoring Committee (DMC) Analysis: An independent DMC will review descriptive summaries of accumulating safety, subject disposition and limited efficacy data at 3 timepoints throughout the study. The summaries provided will be a subset of those described in this SAP. the composition, roles and responsibilities of the DMC are 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.

Interim Analysis: No formal interim analysis will be performed. See section 13.0.

3.   Study Objectives

3.1.   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 (ICR) of tumour assessments.

3.2.   Secondary Objective(s)

3.2.1.   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 ICR;
- Investigator assessed PFS (based on a local review);
- Patient reported outcomes for health related quality of life;
- Safety and tolerability.

3.2.2.   Other Objectives

The other objectives of this study are as follows:

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

4. Study Details/Design

4.1. Brief Description

This study is an open-label, phase III study. 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 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) (1-2, more than 2), and prior treatment with pertuzumab (yes, no).

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 adverse events (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.

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. Enrolment is targeted for at least 423 patients, resulting in 282 patients in the SYD985 group and 141 in the physician's choice group.

4.2. Patient Selection

The study population will consist of female patients >= 18 years of age at informed consent with HER2-positive unresectable locally advanced or metastatic breast cancer.

4.2.1. Inclusion Criteria

See protocol section 8.1.1.

4.2.2. Exclusion Criteria

See protocol section 8.1.2.

4.3. Determination of 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.

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.

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.

4.4. Treatment Assignment and Blinding

After signing the "HER2 testing" or "Study" informed consent form (ICF), the investigator (or authorized delegate) will enter the electronic eCRF to obtain a patient number.

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). 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 via Balance/RAVE. 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) (1-2, more than 2), and prior treatment with pertuzumab (yes, no).

Blinding of treatment assigned is not applicable as this is an open-label study.

4.5. Administration of Study Medication

4.5.1. SYD985 Treatment

SYD985 1.2 mg/kg will be administered every three weeks (± 3 days) by intravenous infusion. Dose delays and dose reductions are allowed as described in the protocol section 9.5.

4.5.2. Physician's Choice Treatment

Physician's choice therapy options:

1. Lapatinib + Capecitabine
2. Trastuzumab + Capecitabine
3. Trastuzumab + Vinorelbine
4. Trastuzumab + Eribulin

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

4.6. Study Procedures and Flowchart

See Protocol Section 1.1 for the study flowchart detailing assessments (including specific notes for assessments) and procedures by visit.

The visit structure and allowable windows are as follows:

	Screen-ing	Cycle 1				Cycle 2			Cycle 3	Cycle 4			Cycle 5 Onwards	Treatment Disc.	Survival Follow-up
Visit Day	D-28 to -1	D1	D2	D8	D15	D1	D8	D15	D1	D1	D2	D15	D1	28-42 days after last dose of study treatment or before the start of anticancer treatment, whichever comes first	Every 3 months after last contact
Visit Window (Days)				± 1	± 1	± 3	± 1	± 1	± 3	± 3		± 3	± 3		± 14

D = Day; Disc = discontinuation.

In addition, there are notes to the study flowchart detailing variations to the above visit windows for certain assessments, these are specified below.

Note 2: Day 1 assessments are to be done prior to study drug administration;

Note 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;

Note 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;

Note 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;

Note 10: Ophthalmological examination (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) as well as left ventricular ejection fraction (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;

Note 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;

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.

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.

5. Endpoints

5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on ICR of tumour assessment according to Response Evaluation Criteria for Solid Tumours (RECIST) 1.1 (Eisenhauer, 2009).

5.2. Secondary Efficacy Endpoints

- OS;
- ORR on the basis of the blinded ICR;
- Investigator assessed PFS (based on local review);
- Patient reported outcomes for health related quality of life.

5.2.1. Other Efficacy Endpoints

- TTR;
- DOR;
- CBR.

5.3. Exploratory Endpoints

- Exposure/response and exposure/safety relationships (as described in section 2.1 not to be detailed in this SAP).

5.4. Pharmacokinetic Endpoints

To evaluate the pharmacokinetics of SYD985.

5.5. Safety Endpoints

- Incidence and severity of (serious) adverse events (AEs) and (serious) Adverse Events of Special Interest (AESIs).
- Changes in LVEF and ECG and ophthalmological examinations.
- Changes in vital signs and weight.
- Changes in Eastern Cooperative Oncology Group (ECOG) performance status.
- Changes in laboratory parameters, including cardiac biomarkers.
- Formation of SYD985 ADAs.

6. Analysis Sets

6.1. Screened Set

The Screened Set (SS) will include all patients who have signed informed consent (HER2-ICF and/or Study-ICF). Unless specified otherwise, this set will be used for the summaries of patient disposition and to list disposition and randomization data and screen failure data at the end of the appropriate listing (informed consent, patient eligibility, demographics and (serious) adverse events).

6.2. 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. The FAS will be used for all analyses of efficacy and for the protocol deviations, patient eligibility, baseline and efficacy listings.

6.3. Safety Analysis Set

The Safety Analysis Set (SAS) includes all patients who received at least one (partial) 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. The SAS will be used for all analyses of safety endpoints and the safety listings.

6.4. Per-Protocol Set

The Per-Protocol Set (PPS) will include the subset of the patients in the FAS who were administered at least one (partial) dose of study medication and who do not have any major protocol deviations or multiple minor deviations. Protocol deviations or conditions leading to exclusion from the PPS are specified in section 6.6. Patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The PPS will be used for baseline summaries, a secondary analysis of the primary endpoint of PFS and a number of additional efficacy endpoints as described in SAP section 9.0.

6.5. Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all patients who received at least one (partial) dose of the study drug SYD985 and for whom at least one PK parameter can be calculated. The PKS will be used for the analyses of all PK endpoints. The final PKS will be determined by the ▮▮▮▮▮▮▮▮ study PK Scientist.

6.6. Protocol Deviations

Protocol deviation management at ▮▮▮▮▮▮▮▮ is detailed in the Protocol Deviation and Non-compliance Management Plan.

Two protocol deviation summaries and corresponding listings will be provided: 1) all major deviations; 2) major protocol deviations leading to PPS exclusion.

The list of major protocol deviations leading to PPS exclusion includes at least the following deviations:

- Patients younger than 18 years old.
- Violation of inclusion criteria 2: Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer.
- Violation of inclusion criteria 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.
- Violation of inclusion criteria 8: adequate organ function.
- Violation of exclusion criteria 3: history of keratitis.
- Failure to obtain ICF.
- Treatment allocation error (patient is randomized to SYD985 but receives the Physician's Choice or vice versa), or treatment error (switch of treatments SYD985 to Physician's Choice or vice versa, during the study).

The final list of patients that are to be included in the PPS will be determined at the Data Review Meeting (DRM). The DRM will occur when all or nearly all queries have been resolved and the database is near to final. For the DRM meeting, a DRM Preparation Plan will be prepared. This plan will detail further the types of protocol deviation criteria and will include, as a minimum: 1) the exact criteria which will be used to determine if a patient will be excluded from the PPS; 2) the listings which will be prepared for sponsor review in order to determine which patients to exclude from the PPS. Details of patient specific exclusions from the PPS will be detailed in the DRM Highlights document.

Note: a separate summary and listing of COVID-19 related protocol deviations will be provided using the FAS. COVID-19 related protocol deviations are reviewed and confirmed during the scheduled protocol deviation review meetings as described in the Protocol Deviation and Non-compliance Management Plan.

7. General Aspects for Statistical Analysis

7.1. General Methods

- SAS version 9.3 or higher will be used.

- Phoenix WinNonLin version 6.4 or higher will be used for PK parameter derivation.

- Analysis datasets used for statistical analyses will be developed according to CDISC (Clinical Data Interchange Standards Consortium) Analysis Data Model (ADaM) Version 2.1 corresponding to Version 1.0 of the Analysis Data Model Implementation Guide (ADaMIG). Documentation (DEFINE.xml) will be provided.

- Unless otherwise specified, summaries will be presented for each treatment group, 'SYD985' then 'Physician's Choice'. A 'Total' column will be added to the baseline tables.

- Continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of patients.

- Unless stated otherwise, the calculation of percentages will be based on the total number of patients in the population of interest. Thus counts of missing observations will be included in the denominator and presented as a separate category.

- Multiple assessments on the same day (planned, repeat) will not be included in summary tables unless specified otherwise, but will be included in the listings. If there are multiple valid results at a given visit (i.e. the same day), e.g. a repeated lab test within a visit, the earliest value will be used.

- In general, unscheduled visit data will be listed but not included in the summary tables by visit/timepoint. Unscheduled data will be included to identify the worst case post-first dose for safety shift tables.

- Time to event data (e.g. PFS, OS) will be analyzed using Kaplan-Meier survival estimates. Summary statistics will include median, 25th, and 75th percentile survival times and corresponding 95% confidence intervals (CIs).

- Unless otherwise specified, listings will be sorted by treatment group 'SYD985', physician's choice – in the order: 'Lapatinib + Capecitabine', 'Trastuzumab + Capecitabine', 'Trastuzumab + Vinorelbine', 'Trastuzumab + Eribulin', patient number and assessment date and time.

- All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings. Screen failure data will be included at the end of the appropriate listings and labelled 'Screen Failures'.

- Missing records will be omitted from the listings, and missing data within a record will be left blank.

7.2. Key Definitions

Study day is the day relative to the date of first dose of study medication where Day 1 is the day of study medication.

The first dose date is defined as the first non-missing date where a non-zero dose of study medication was recorded.

The last dose date is defined as the last non-missing date where a non-zero dose of study medication was recorded.

Unless otherwise specified, baseline is the last non-missing observation before or on the start of study medication, which is expected to be Day 1 of Cycle 1 (pre-dose), or screening if the Day 1 data are not available.

7.3. Missing Data

Missing data will be treated as missing except for adverse events where toxicity grade and relationship to study drug are missing (see SAP section 12.1).

Incomplete start dates of adverse events or prior medication or concomitant medication will be imputed according to the following conventions:

Missing item	Condition	Imputed date
Day	MMMYYYY = Date of first dose	Date of first dose
	MMMYYYY < Date of first dose	Date of IC or 01MMMYYY, whichever is the later
	MMMYYYY > Date of first dose	01MMMYYYY
Day and month	YYYY = Date of first dose	Date of first dose
	YYYY < Date of first dose	Date of IC or 01JANYYYY, whichever is the later
	YYYY > Date of first dose	01JANYYYY
Year	DDMMM	Date of first dose
Day, month, year	None	Date of first dose

IC = Informed Consent

For incomplete diagnosis dates, a missing day will be imputed as 01 and a missing month as JUL. If the date is missing entirely, there will be no imputation. No imputation of incomplete or missing dates for any other historical data will be done.

Note: a listing of missing assessments and a listing of missing visits due to COVID-19 will be provided. The FAS will be used.

7.4. Visit Windows

In general, if multiple (planned) assessments fall within the same window, the assessment closest to the scheduled/planned day will be used in summaries and analysis.

Visit windows for unscheduled visits are defined as follows:

Planned Visit/Assessment Day		Window (Days) for the Planned Visit/Assessment
Cycle	Day	(related to cycle)
1	1	1
	2	2 - 4
	8	5 - 11
	15	12 - start next cycle*
2	1	1 - 4
	8	5 - 11
	15	12 - start next cycle*
3	1	1- start next cycle*
4	1	1
	2	2 - 4
	15	5 - start next cycle*
5 (and onwards)	1	1-start next cycle*
Treatment disc.		Visit – 30 days after visit

*Or treatment discontinuation visit, if this was the last cycle; the next cycle is defined as Day 1 of the next cycle. If an assessment is in the middle of a window, the earliest assessment will be selected e.g. Cycle 1 Day 8, the visit window is 5 -11 days. There is an assessment on Day 7 and another assessment on Day 9 so both are +/- 1 day from day 8, the Day 7 assessment will be used. FU = follow up.

For certain assessments there are the following specific windows:
- Weight on Cycle x Day 1: day -7 to day 1
- Haematology/chemistry/cardiac troponin and urinalysis (central and local) on Cycle 1 Day 1: day -5 to day 1
- Haematology/chemistry/cardiac troponin and urinalysis (central and local) on Cycle 2 (and onwards) Day 1: day -3 to day 1
- Ophthalmological examinations (slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry) on Cycle x Day 1: day -7 to day 1
- LVEF on Cycle x Day 1: day -7 to day 1

Tumour measurement analysis is being performed on the basis of actual assessment time points, windows are not applicable.

PK sampling analysis is being performed on the basis of actual sampling time points, windows are not applicable.

As previously described, in addition to the current SAP, additional SAP(s) will be prepared to analyse immunogenicity, ECG data therefore possible visit windows for these parameters will not be specified in this SAP.

7.5. Pooling of Centers

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

7.6.   Subgroups

Both PFS by ICR and OS based on the FAS will be sub-analyzed for the following categories: age, world region (randomization stratum), race, ECOG, hormone receptor status, disease involvement, number of previous regimens for advanced and/or metastatic disease, brain lesions at screening, T-DM1 pre-treatment, pertuzumab pre-treatment, pertuzumab and T-DM1 pre-treatment. See SAP section 9.4 for further details of categorization and statistical methods.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Patient Disposition, Withdrawals and Screen Failures

The study disposition summary table will include the number and percentage of patients in each of the analysis sets for the screened set. This summary will also include the number of patients screened, randomized and screen failures (including reason for screen failure, ie failed criteria). The table will be presented by treatment group (the 4 subgroups for Physician's Choice will be summarized separately) overall and by country.

In addition, a separate disposition summary for the FAS will include the number and percentage of patients who discontinued treatment (including the reason for treatment discontinuation) and who discontinued from the study (including the reason for study discontinuation) by treatment group. The disposition table will also include randomization strata, country, how many patients received which Physician's Choice treatment regimen and the number of patients attending each cycle to determine the number of cycles received. This will be determined by the study drug administration data – a non-missing dose greater than zero for any day within a cycle will be counted. Cycles received will be presented as a categorical and continuous variable. The table will be presented overall and by country.

Disposition (including reasons for exclusion from analyses sets), randomization (planned from Balance/RAVE and actual as captured on the eCRF; any differences will be flagged) and eligibility criteria (including failed criteria for screen failures), signing of Study-ICF date, signing of HER2–testing-ICF date and protocol version will be listed. Screen failure data will be listed in the appropriate listing and will appear at the end of the listing.

Patients impacted by COVID-19 related treatment/study discontinuations will be listed separately using the FAS. The 'End of Treatment' and 'Discontinuation from Study' eCRF data will be used. E.g. if End of Treatment reason is 'Adverse Event', the AE coding is checked for 'COVID'. Similarly, the 'other, specify' comments are checked for 'COVID' for other treatment/study discontinuation reasons (e.g. 'Withdrawn Consent', 'Lost to Follow Up', 'Other').

Major protocol deviations will be summarized by treatment group using the FAS. All protocol deviations will be listed by treatment group, patient number, deviation type (major or minor) and date.

8.2. Demographic and Baseline Characteristics

Age (years) at signing ICF (as collected on the eCRF), weight (kg) and height (cm) will be summarized by treatment group using summary statistics for continuous variables; demography (child bearing status, race, ethnicity) will be summarized as categorical variables. Demography data will be summarized for the FAS, PPS and SAS.

The following conversions will be used:

Height (in cm) = height (in inches) * 2.54
Weight (in kg) = weight (in lbs) * 0.4536
Body Mass Index (BMI) (kg/m^2) = Weight(kg)/[Height(m)^2]

Demographics will be summarized as described above using the SAS comparing patients who started treatment before vs. during the COVID-19 pandemic. For Italy and Singapore, a cut-off date of 01-Jan-2020 will be used. That is if the first dose date is before 01-Jan-2020, then a patient will have started

treatment before the pandemic vs. a first dose date of the 01-Jan-2020 or later a patient will be considered as having started treatment during the pandemic. For all other countries, a cut-off date of 01-Mar-2020 will be used and applied based on first dose date as described above.

Assessment of disease at baseline will be summarized by treatment group including cancer type, histological classification, time from diagnosis to study entry in months ([derived as study IC date – diagnosis date + 1]/30.5), time from diagnosis of locally advanced or metastatic disease to study entry in months ([derived as study IC date – diagnosis date of locally advanced or metastatic disease + 1]/30.5) (see SAP section 7.3 which details how partial or missing diagnosis dates will be imputed), stage, disease type (locally advanced or metastatic), metastatic sites, visceral/non-visceral disease, brain metastases and hormone receptor (HRr) status for ER and PR, if available. Overall HRr status will be derived: if ER or PR is positive then HRr status is positive; if ER and PR is negative then HRr status is negative. Central HER2 status assessment will also be summarized. The FAS, PPS and SAS will be used. All other baseline characteristic data (e.g. previous treatment of brain metastases etc) will be listed for the FAS.

Tables will be presented by treatment group (the 4 subgroups for Physician's Choice will be summarized separately) overall and by country.

Brain scan and whole body bone scan data will be listed and sorted by patient number, treatment group and examination date.

8.3. Medical History and Concomitant Diseases

Medical history consists of any significant events (conditions or diseases) that were present before signing IC. Medical history/concurrent illness will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) latest version. Medical history frequencies will be summarized by treatment group and will be ordered by descending frequency within the SYD985 treatment group by system organ class (SOC) then, within a SOC, by overall descending frequency of preferred term (PT). If incidence for more than 1 term is identical, they will be sorted alphabetically. The Child-Pugh classification for hepatic impairment will be summarized with the medical histories. The FAS and SAS will be used. Medical history conditions, as recorded on the eCRF at screening, will be listed for the FAS. The medical history listing will be sorted by treatment group, patient number and onset date.

8.4. Medication

8.4.1. Prior Systemic Therapy Related to Study Indication

Prior systemic therapies related to study indication (as recorded on the eCRF page 'PRIOR SYSTEMIC THERAPY (RELATED TO STUDY INDICATION)') in the locally advanced/metastatic setting will be presented in tabular form using Anatomical Therapeutic Chemical (ATC) classification system level 2 (therapeutic subgroup) and preferred name via the World Health Organization Drug classification Dictionary (WHO DRUG) latest version. All medications will be sorted by descending frequency within the SYD985 treatment group at ATC level 2 and then, within ATC level 2, by descending frequency of preferred name. If incidence for more than 1 term is identical, they will be sorted alphabetically. The number and percentage of patients who took at least one drug within each specific preferred name will be presented. Patients will only be counted once if they are taking more than one medication or take the same medication more than once.

In addition, for the prior systemic therapy related to the study indication, the number of prior treatment regimens (categorized as 1–2, 3-4, 5-8, >=9 and also summarized as a continuous variable), the number

of prior regimens in metastatic setting (categorized as 1–2, 3, >=4 and also summarized as a continuous variable), the number of HER2 targeting regimens in the metastatic setting (categorized as 1–2, >=3) and prior treatment regimens in the metastatic setting (Trastuzumab + Pertuzumab + Taxane (taxane can include docetaxel and paclitaxel), Trastuzumab + Pertuzumab, Trastuzumab + Capecitabine, Trastuzumab + Lapatinib, Trastuzumab + Vinorelbin, Trastuzumab + Eribulin, (Ado)trastuzumab-Emtansine, Lapatinib + Capecitabine) will be summarized by treatment group. Tables will be presented by treatment group (the 4 subgroups for Physician's Choice will be summarized separately) overall and by country.

Medication will be listed for the FAS and will be sorted by treatment group, patient number and start date. The FAS and SAS will be used for medication summaries.

8.4.2. Prior Medication (not Related to Study Indication)

Prior medications (medications where the stop date is prior to the date of first dose of study medication) not related to study indication will be listed.

All prior medications will be listed including the derived study day relative to first dose (for both start and stop dates) and a flag for prior medications.

8.4.3. Concomitant Medication

Concomitant medications (medications starting on or after the start of study treatment and continuing after the start of study treatment) will be presented in tabular form using ATC classification system level 2 (therapeutic subgroup) and ATC level 4 (chemical subgroup). All medications will be sorted by descending frequency within the SYD985 treatment group at ATC level 2 and then, within ATC level 2, by descending frequency of ATC level 4. If incidence for more than 1 term is identical, they will be sorted alphabetically. The number and percentage of patients who took at least one drug within each specific ATC level 4 will be presented. Patients will only be counted once if they are taking more than one medication or take the same medication more than once. SAP section 7.3 describes how to deal with partial medication start and stop dates. Section 10 of the protocol details the excluded prior and concomitant medications.

Medication will be listed for the FAS and will be sorted by treatment group, patient number and start date. The FAS and SAS will be used for medication summaries.

8.4.4. Other Therapies

Prior radiotherapy and surgery (related to study indication) will be listed and sorted by treatment group, patient number and date (first dose date for prior radiotherapy and date of surgery).

8.5. Extent of Exposure

8.5.1. SYD985

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

The extent of exposure will be examined by summarizing the variables below:

- Total dose (mg) of SYD985 administered overall.
- Number of cycles started (where a non-null value for 'Total Calculated Dose (mg)' is captured on Day 1. Presented as a categorical (1-4 cycles, > 4 cycle; the final categories will be determined based on the final distribution of the data) and a continuous variable.
- Duration of exposure (expressed in months and weeks) for SYD985. This is calculated as follows:

    [(last dose date – first dose date) + 22] / 30.5 (for months) or 7 (for weeks)

    Note, as the last dose may continue to cause an effect for at least 3 weeks (dosing schedule is every 3 weeks), 21 days will be added to the interval between first dose and last dose (in addition to 1 day for cases where the first and last dose may have been the same date). Death date will be used if death occurs earlier.
- Dose intensity (mg/weeks) overall. Computed as the ratio of the total actual dose received and duration of exposure.
- Patient years for exposure.
- SYD985 infusion rate reductions, interruptions, dose reductions and dose delays overall. A patient is only counted once. If there are any rate reductions, interruptions, delays or dose reductions a patient will be counted as 'Yes'. The number of rate reductions, interruptions, dose reductions and dose delays per patient will also be summarized. The categories for rate reductions, interruptions and dose reductions are '0', '1', '2', '>2'. The categories for dose delays are '0', '1-3', '4-6' and '>6'. Dose modifications (dose delay and/or reduction) will be also summarized as described above using the categories for dose delays.

All SYD985 administration data will be listed and will include whether a patient is continuing to the next cycle.

A swimmer plot will be provided for duration of treatment in weeks.

8.5.2. Physician's Choice

The extent of exposure will be assessed by summarizing for, capecitabine, vinorelbine (oral and intravenously (IV)), eribulin and trastuzumab as described above for SYD985: total dose administered, total number of cycles started, duration of exposure and patient years. For the oral administration of vinorelbine, total dose administered will be determined based on dose, regimen and the number of days missed. For lapatinib (administered daily orally), total dose administered will be based on dose and number of days missed.

All lapatinib, capecitabine, vinorelbine (oral and IV), eribulin and trastuzumab data will be listed and will include whether a patient is continuing to the next cycle.

Swimmer plots will be provided for duration of each physician's choice treatment in weeks.

8.6. Treatment Compliance

Not applicable.

9. Efficacy

The efficacy analysis will be performed using the FAS. The PPS will be used for a secondary analysis of the primary endpoint.

9.1.1. Primary Analysis of the 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 (in months) 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).

PFS (months) = [(Date of progression/death – date of randomization) + 1] / 30.5

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" prior to the date when a new therapy for cancer is started, 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 first missing assessment. If disease progression occurs after one missed tumour assessment, the event will be counted at the respective event date. These rules are summarized in the table below:

Situation	Date of Progression or Censoring	Outcome
No baseline tumour assessments	Randomization	Censored
Progression documented between scheduled visits	Date of radiological assessment of measured lesions	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions prior to start new treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

Death or progression after more than one missed tumor assessment	Date of last radiological assessment of measured lesions prior to first missing assessment	Censored

The primary efficacy endpoint PFS will be analyzed based on the data observed in the FAS population. 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) (1-2, more than 2), and prior treatment with pertuzumab (yes, no). Pooling of strata will be considered depending on the counts of patients in the randomization strata and specifically if there are any low counts in any stratum. 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 in tabular form by treatment group. The table will be presented overall and by country. Kaplan Meier plots will be provided; treatment group will be differentiated with a different line style.

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.,

$H_{01}: S_{1T(t)} = S_{1R(t)}$ vs. $Ha1: S_{1T(t)} \neq S_{1R(t)}$, 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 $S_{1R(t)}$ 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 (progression or death) at any timepoint.

versus

H_{a1}: there is a difference between the populations in the probability of an event (progression or death) at some timepoint.

A stratified Cox regression analysis will be used to estimate the hazard ratio (HR) of PFS, along with 95% CIs (using the same strata information as above). The stratification variables will be included as covariates in the model statement and ties=exact (or ties=efron) will be included.

9.1.2.   Secondary Analysis of the Primary Endpoint

The analysis as described in section 9.1.1 as for the primary analysis will be repeated using the PPS and presented overall only, not by country.

9.1.3.   Sensitivity Analyses of the Primary Endpoint

The analysis as described in section 9.1.1 will be repeated as follows (overall only, not by country, the FAS will be used):

1. If there are any treatment allocation errors or mis-stratification errors at randomization, analyze according to actual treatment and strata.

2. Analyze without the stratification factors to derive the p-value and hazard ratio.
3. Analyze using the date of progression calculated as the earlier of the IRC or investigator assessments.
4. Analyze with the date of progression shifted to the day after the last preceding tumour evaluation where progression was known not to have occurred, ie the worst case.

9.1.4. Additional Summary of the Primary Endpoint

PFS by ICR will be summarized for SYD985 and the 4 Physician's Choice subgroups separately using the FAS. No inferential analyses will be completed.

9.2. Secondary Efficacy Endpoint(s) and Analyses

The secondary efficacy endpoints of this study are overall survival, ORR based on blinded ICR, investigator assessed PFS according to the RECIST data captured on the eCRF (local review) and patient reported outcomes for health related QoL.

9.2.1. Overall Survival

Overall survival is defined as the time (in months and years) from date of randomization to date of death due to any cause.

OS (Months) = [(Date of death – date of randomization) + 1] / 30.5
OS (Years) = [(Date of death – date of randomization) + 1] / 365.25

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.

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}: $S_{2T(t)} \neq S_{2R(t)}$, 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).

or in words

H_{02}: there is no difference between the populations in the probability of an event (death) at any timepoint.

versus

H_{a2}: there is a difference between the populations in the probability of an event (death) at some timepoint.

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 survival distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% CIs will be presented in tabular form by treatment group. The stratified Cox regression analysis will be used to estimate the HR of OS, along with 95% CI. In addition, the 1-year survival rate and corresponding 95% CI will be estimated using the Kaplan-Meier approach. The table will be presented overall and by country. Kaplan Meier plots will be provided; treatment group will be differentiated with a different line style.

The OS data will be listed by treatment group and patient number.

A sensitivity analysis of OS as described above will be repeated using the PPS (overall only, not by country).

A further summary will compare SYD985 to each of the 4 Physician's Choice subgroups separately using the FAS. No inferential analyses will be completed.

9.2.1.1. *Survival Follow Up*

Survival follow-up data including progression, progression date and subsequent anti-cancer therapy (SACT) will be collected at treatment discontinuation and then every 3 months after last contact. Time since discontinuation of study treatment (last dose date) to progression date, first SACT date and second progression will be derived and summarized for the FAS as follows:

1. Time to progression (days) = progression date - last dose date + 1 (for patients who discontinued treatment for a non-progressive disease reason from the 'End of Treatment' eCRF page).
2. Time to start first SACT (days) = first SACT date - last dose date + 1 (for all patients)
3. Time to 2nd progression (days) = progression date - last dose date + 1 (for patients who discontinued treatment due to disease progression from the 'End of Treatment' eCRF page).

The survival follow-up data, including reason for death, will be listed for the FAS.

9.2.2. Objective Response Rate

Objective response rate is defined as the percentage of patients with ICR-assessed best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 (i.e. 'Responders'). 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.

If a best overall tumour response of CR or PR is obtained at any post-first dose timepoint, then a patient is considered a 'Responder'; if best overall response is 'Stable Disease', 'Progressive Disease', 'Non-CR/Non-PD' or 'Not evaluable', then a patient is considered a 'Non-responder'.

ORR will be calculated based on the FAS population. The percentage of patients with a response will be summarized 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. The table will be presented overall and by country. The analysis described above will be repeated using the PPS (overall only, not by country). This will be considered a sensitivity analysis.

The following sensitivity analysis will also be calculated using the FAS (overall only, not by country):

- Confirmed ORR by ICR. A response will be considered confirmed by a second assessment at least 4 weeks after first assessment.
- ORR as assessed by local review.
- Confirmed ORR by local review.

For the local review, (as captured on the eCRF page 'RECIST 1.1 OVERALL TUMOUR RESPONSE (LOCAL REVIEW), 'Overall Tumour Response' variable) the same rules apply as for ICR-assessed best response. A response will be considered confirmed by a second assessment at least 4 weeks after first assessment.

Further summaries of ORR and confirmed ORR will compare SYD985 to each of the 4 Physician's Choice subgroups separately using the FAS. No inferential analyses will be completed.

The RECIST 1.1 target and non-target lesion measurements and new lesion as collected on the eCRF (local review) and the ICR data will be listed separately by treatment group, patient number and evaluation date. Study day will be included on the listings.
Overall tumour response (local review and as reported by ICR) will be listed in a similar manner. Further, any differences in overall tumour response between central and local review of RECIST 1.1 assessments will be listed separately by treatment group, evaluation date and review type ('ICR' then 'Local'). Note – all records per patient will be listed if there are any differences in overall tumour response between the ICR and local review.

9.2.3.   Investigator Assessed PFS

Investigator assessed PFS, based on local review data captured in the eCRF, is defined as the time (in months) from the date of randomization to the date of first documented investigator-assessed disease progression according to RECIST 1.1 (as captured on the eCRF page 'RECIST 1.1 OVERALL TUMOUR RESPONSE (LOCAL REVIEW), 'Overall Tumour Response' variable) or death due to any cause (whichever occurs earlier). Handling of missing values will be as described for the primary endpoint (see SAP section 9.1.1).

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. The table will be presented overall and by country. Kaplan Meier plots will be provided; treatment group will be differentiated with a different line style. The PFS analysis described above will be repeated using the PPS (overall only, not by country).

A summary will compare SYD985 to each of the 4 Physician's Choice subgroups separately using the FAS.

Investigator assessed PFS will be determined using the progression date from the Survival Follow Up eCRF page for patients who discontinued treatment for a non-progressive disease reason. Patients with no progression in follow up will be censored at the last follow up date. If a patient discontinues treatment due to PD, but the last local RECIST evaluation was not PD (i.e. clinical PD). PFS will be censored at the

date of treatment discontinuation from the 'End of Treatment' eCRF. The PFS analysis will be completed as described above for investigator assessed PFS using the FAS.

Any differences in ICR and investigator assessed PFS will be flagged in the listing investigator assessed PFS listing.

9.2.4. Patient Reported Outcomes

Patient reported outcomes for health related quality of life are collected with the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 questionnaire (version 3.0) (Aaronson et al, 1993) along with the disease-specific breast cancer module (EORTC QLQ-BR23) (Sprangers et al, 1996) on Day 1 of Cycles 1 – 5 then every 2nd cycle and at treatment discontinuation. 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 (Fayers et al, 2001).

The QLQ-C30 (version 3.0) is composed of multi-item scales and single-item measures. These include 1 global health status/QoL scale, 5 functional scales, 9 symptom scales/items as follows:

Global Health Status/QoL Scale
- Global Health Status/QoL

Functional Scales
- Physical Functioning
- Role Functioning
- Emotional Functioning
- Cognitive Functioning
- Social Functioning

Symptom Scales/Items:
- Fatigue
- Nausea and Vomiting
- Pain
- Dyspnoea
- Insomnia
- Appetite Loss
- Constipation
- Diarrhoea
- Financial Difficulties

The breast cancer specific module QLQ-B23 has 4 functional scales, 4 symptom scales/items as follows:

Functional Scales
- Body Image
- Sexual Functioning
- Sexual Enjoyment
- Future Perspective

Symptom Scales/Items:
- Systemic Therapy Side Effects

- Breast Symptoms
- Arm Symptoms
- Upset by Hair Loss

The number of patients completing each patient questionnaire in full and the number of missing or incomplete items will be summarized by treatment group for each scheduled assessment timepoints for the EORTC QLQ-C30 and EORTC QLQ-B23 questionnaires. The table will include the number of completed and missing questionnaires and items. The denominator for the percentage of completed/missing questionnaires will be the number of patients expected per visit (from eCRF page 'Visit Date' and the response is 'Yes' for 'Was this visit performed?')

Descriptive statistics will be used to summarize the scale scores/items for the EORTC questionnaires at each scheduled assessment timepoint. Additionally, change from baseline in the scale scores/items at the time of each assessment will be summarized. Patients with an evaluable baseline scale scores/items and at least one evaluable post-baseline scale score/item during the treatment period will be included in the change from baseline analyses. Both transformed and raw scores will be presented.

The global health status/QoL scale score of the EORTC QLQ-C30 is identified as the primary patient-reported outcome variable of interest. The change from baseline in the global health status/QoL scale transformed score will be analyzed using a mixed model repeated measurement (MMRM) approach. The model will use the change from baseline in the reported QoL scale score as the dependent variable and will include a fixed effect of treatment group, randomization strata, cycle, baseline QoL scale score, and a treatment-by-time interaction. The baseline QoL scale score will be included in the model as a covariate. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. Patient is a random effect. An unstructured (general) covariance structure will be assumed initially to model the within-patient errors; however, other covariance structures will be tested and may be used in the final model if a better fit is evident. The least squares (LS) means, differences between LS means, 95% CIs for each difference and the p values from model effects will be reported to evaluate the treatment effect. LS means ± 95% CI will be presented by visit graphically; treatment group will be differentiated with a different line style. The inferential analysis will be presented overall and by country using the FAS.

The inferential analysis described above will be repeated using the PPS (overall only, not by country). This will be considered a sensitivity analysis.

In addition, a further sensitivity analysis will be conducted - the distribution of time to definitive 10% deterioration in the global health status/QoL transformed scale score in months will be assessed in the treatment groups. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% worsening of the corresponding scale score relative to baseline (without further improvement above the threshold) or death due to any cause (whichever occurs earlier).

Time to 10% deterioration in global health status/QoL score (Months) = [(Date of 10% deterioration/date of death – date of randomization) + 1] / 30.5

If a patient has not had an event, time to deterioration will be censored at the date of the last non-missing global health status/QoL score. If a patient did not have any baseline QoL assessment, time to deterioration will be censored at the date of randomization plus 1 day. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10% deterioration along with

two-sided 95% CI. Additionally, time to definitive deterioration with different cut off definitions (e.g. 5%, 15%) may be analyzed. A stratified Cox regression will be used to estimate the hazard ratio, along with two-sided 95% CI. Kaplan Meier plots will be provided; treatment group will be differentiated with a different line style.

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 and will be analyzed descriptively as detailed above.

A summary will compare global health status/QoL score between SYD985 to each of the 4 Physician's Choice subgroups separately using the FAS.

9.3. Other Efficacy Endpoint(s) and Analyses

Other efficacy endpoints are:

- To describe Time to Response (TTR) in each treatment group;
- To describe Duration of Response (DOR) in each treatment group;
- To describe Clinical Benefit Rate (CBR) in each treatment group.

9.3.1. Time to Response (TTR)

TTR is the time between the dates of randomization until first documented response (CR or PR) according to RECIST 1.1. All patients in the FAS 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 or death due to any cause) or at the date of last adequate tumour assessment date otherwise.

TTR (months) = [(Date of PR/CR – date of randomization) + 1] / 30.5

TTR will be analyzed based on the data observed in the FAS population and will be determined primarily by ICR of tumour assessment (an analysis based on investigator tumour assessment will also be performed). The survivor distribution of TTR will be estimated per treatment group using the Kaplan-Meier method. The median TTR along with 95% CI will be presented by treatment group in tabular form. TTR will also be evaluated using all responses (confirmed and unconfirmed) for both the ICR and local review.

Any differences in ICR and investigator assessed TTR will be flagged in the listing.

9.3.2. Duration of Response (DOR)

DOR 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).

DOR (months) = [(Date of progression/death – date of first PR/CR) + 1] / 30.5

DOR will be analyzed based on the data observed in the FAS population and will be determined primarily by ICR of tumour assessment (an analysis based on local review 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.

Any differences in ICR and investigator assessed DOR will be flagged in the listing.

9.3.3. Clinical Benefit Rate (CBR) based on Best Overall Response

The CBR is defined as the percentage of patients with:

- measurable disease with:
  - CR
  - PR
  - SD (SD for 6 months or longer)

- non-measurable disease with:
  - CR
  - non-CR/non-PD (non-CR/non-PD for 6 months or longer).

according to RECIST 1.1.

Duration of clinical benefit for patients with SD or non-CR/non-PD (to be at least 6 months defined as 183 days) will be determined by the randomization date until a response of PD is first recorded. Note if a later SD or non-CR/non-PD follows NE it is assumed that SD continued.

Duration of CB (days) = (Date of first PD – randomization date) + 1

CBR will be analyzed based on the data observed in the FAS population and will be determined primarily by ICR of tumour assessment (an analysis based on local review will also be performed).

Patients with missing overall responses (but who do have a post-first dose record for overall tumour response) will be treated as CBR = 'No', i.e. they will be included in the denominator when calculating the percentage.

CBR will be summarized for the two treatment groups using descriptive statistics.

9.3.4. Percentage of Patients with Reduction in Target Lesions

The analysis described in section 9.3.3 will be repeated using the percentage of patients with reduction of target lesions (sum of diameters). This analysis will only apply to patients who had measureable disease at baseline. The denominator will be all patients in the FAS with measurable disease at baseline.

Additionally, a waterfall plot for best percentage change from baseline in the sum of target lesion longest diameters will be provided by treatment group. The Y axis will be percent change from baseline and patient number on the X axis. A positive result indicates an increase in tumor size; a negative result indicates a decrease (shrinkage). Response (confirmed responder, unconfirmed responder, SD, and PD) as assessed by ICR will be differentiated by different bar styles. The FAS will be used.

9.4. Subgroup Analysis of Efficacy Endpoints

Subgroup analyses will be performed to evaluate the associations between baseline covariates and the primary efficacy endpoint PFS and OS (months) for the FAS population using forest plots. The following subgroups will be investigated:

- Age (Less than 65 yrs, >= 65 yrs)
- World region (Europe and Singapore, North America)
- Race (White vs. Non-white and not-disclosed)
- ECOG (0-1, >=2)
- Hormone receptor status (Positive vs. Negative)
- Disease involvement (Visceral vs. Non-visceral)
- Number of previous regimens for advanced and/or metastatic disease (1-2 vs. >2)
- Brain lesions at screening (Yes vs. No)
- T-DM1 pre-treatment (Yes vs. No)
- Pertuzumab pre-treatment (Yes vs. No)
- Pertuzumab and T-DM1 pre-treatment (Yes vs. No)

The forest plots will show 95% CIs for the HR for PFS. CIs will be presented for each subgroup. A 2-sided p-value for the null hypothesis of a HR of 1 will also be presented for each subgroup.

All subgroup analyses will be regarded as exploratory.

10. Pharmacokinetics

The PK set will be used for the pharmacokinetic analysis.

PK parameters will be derived using Phoenix WinNonLin version 6.4 or higher. The TLFs will be done in SAS 9.3. The PK concentrations (all sampling timepoints) and parameters (at Cycles 1, 2 and 4) will be available for total SYD985 (includes SYD985 with a DAR of ≥ 0), conjugated SYD985 (includes SYD985 with a DAR of ≥ 1) and free toxin (SYD986) from the SYD985 treatment group and will be evaluated for PK analysis.

10.1. PK Sampling Schedule

During the study, venous blood samples will be collected at the following timepoints:

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 (Can be used as Cycle 1 Day 21)
		End of infusion
	8	During the visit
	15	During the visit
Cycle 3	1	Pre-dose (Can be used as Cycle 2 Day 21)
		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 (Can be used as Cycle 4 Day 21) (total SYD985 only)
Treatment discontinuation		During the visit

Additional unscheduled PK sampling may be performed. The handling of these data is described in the SAP section 7.1.

10.2. Plasma PK Endpoint

The following PK parameters will be derived for all 3 analytes for Cycle 1, Cycle 2 and Cycle 4 where possible:

- C_{max} - the maximum plasma concentration, (µg/mL for total and conjugated SYD985; pg/mL for SYD986).
- C_{max}_D – dose normalized maximum plasma concentration, ((µg/mL)/(mg/kg) for total and conjugated SYD985; (pg/mL)/(mg/kg) for SYD986).
- T_{max} – time to C_{max}, (h).
- C_{min} - the minimum plasma concentration, (µg/mL for total and conjugated SYD985; pg/mL for SYD986).
- T_{last} – time of last quantifiable concentration for dose interval, (h).
- C_{last} - last quantifiable concentration for dose interval, (µg/mL for total and conjugated SYD985; pg/mL for SYD986).
- AUC_{last} - area under the plasma concentration time curve from zero to the time of the last measurable concentration (µg/mL*h for total and conjugated SYD985; pg/mL*h for SYD986).
- AUC_{tau} - area under the plasma concentration time curve from zero to the end of dosing interval, may need extrapolation (µg/mL*h for total and conjugated SYD985; pg/mL*h for SYD986).
- AUC_{inf} - area under the plasma concentration time curve from zero to infinity, (µg/mL*h for total and conjugated SYD985; pg/mL*h for SYD986).
- AUC_{inf}_D – dose normalized area under the plasma concentration time curve from zero to infinity, ((µg/mL*h)/(mg/kg) for total and conjugated SYD985; (pg/mL*h)/(mg/kg) for SYD986).
- CL – plasma clearance (total and conjugated SYD985 only) (L/h).
- CL_{ss} – plasma clearance at steady state (total and conjugated SYD985 at Cycle 4 only) (L/h).
- V_z – volume of distribution (total and conjugated SYD985 only) (L).
- V_{ss} – steady state volume of distribution (total and conjugated SYD985 at Cycle 4 only) (L).
- λz - terminal rate constant (1/h).
- points λz – number of data points in the regression line for calculating λz.
- λz-Lower – lower data point in the regression line for calculating λz (h).
- λz-Upper – upper data point in the regression line for calculating λz (h).
- $t_{\frac{1}{2}}$ - terminal elimination half-life (h).
- RCmax, RAUCtau and RAUClast – accumulation ratio assessed as the ratios of Cmax, AUCtau or AUClast for Cycle 2 vs. Cycle 1 and Cycle 4 vs. Cycle 1.

10.3. Presentation of Concentration Data

10.3.1. Handling of Missing Data

Missing concentration data for all patients who are administered SYD985 will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of AUC and for the individual plasma concentration versus time curves, the following rules will apply:

Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;

The sampling time of pre-dose samples relative to dosing will also be treated as zero;

Post-dose BLQ values after the first quantifiable timepoint will be set to missing.

If the actual time of sampling is missing, the planned time may be used.

Samples taken outside the sampling windows may be excluded from by-timepoint summary statistics; this will be determined prior to database lock.

For plasma concentration summary the following rules will apply:

Plasma concentrations BLQ in pre-dose samples and in samples taken before the time of the first quantifiable value will be set to zero;

The plasma concentrations BLQ after quantifiable concentration will be set to zero.

No further imputation will be applied to any missing values.

10.3.2.   Listing and Presentation of Individual PK Data

The actual sampling time of PK blood sample collection will be listed for each patient.
All concentrations will be presented in µg/mL units for total and conjugated SYD985, and pg/mL units for SYD986 free toxin.

Individual patient plasma concentration data for total SYD985 (µg/mL), conjugated SYD985 (µg/mL) and SYD986 free toxin (pg/mL) will be listed by patient and timepoint and will be summarized at each timepoint.

Individual patient PK parameters will be listed for the PK set by patient and will be summarized by cycle. Unreliable PK parameters will be listed but flagged and excluded from summary.

Individual patient linear and semi-logarithmic concentration-time plots by analyte (total SYD985 from Cycle 1 to 5 and onwards, conjugated SYD985 and SYD986 free toxin from Cycle 1 to 4 only) will be produced.

10.3.3.   Summary of PK Concentrations

PK concentration data for each analyte will be summarized using the following descriptive statistics: n, number and % BLQ, arithmetic mean, standard deviation, coefficient of variation (CV)%, minimum, median and maximum, geometric mean, CV% for geometric mean.

Mean concentrations of each analyte will not be presented if 50% or more of the actual values at any one timepoint in the terminal phase are BLQ or missing.

Samples taken outside the allowed time windows may be excluded from summarization.
This will be determined prior to database lock. The exclusions will be defined based on the review of protocol deviation log and communicated to the sponsor prior to implementation.

Mean ± standard deviation concentration-time profiles will be presented on linear and log-linear scales vs. nominal time separately for each analyte.

10.3.4.   PK Parameters Derivation

The PK parameters for total SYD985, conjugated SYD985, and SYD986 free toxin will be estimated using concentrations in µg/mL (total and conjugated SYD985) and pg/mL (SYD986) units as follows:

PK Parameters	Parameter Derivation
C_{max} and T_{max}	C_{max} and the corresponding T_{max} will be read directly from individual concentration-time plot for Cycles 1, 2, and 4
C_{min} and T_{min}	C_{min} and the corresponding T_{min} will be determined directly for Cycles 1, 2, and 4
AUC_{last}	AUC_{last} will be calculated using the log-linear trapezoidal interpolation rule for intravenous model for Cycle 1, 2, and 4
AUC_{tau}	AUC_{tau} will be calculated using the log-linear trapezoidal interpolation rule for intravenous model with the possible extrapolation to the end of dosing interval if needed for Cycles 1, 2, and 4, where tau is the 21-day dosing interval
AUC_{inf}	AUC_{inf} will be calculated using the log-linear trapezoidal interpolation rule for intravenous model as $AUC_\infty = AUC_{last} + AUC_{extrap}$. AUC_{extrap} is calculated by the program as: C_{last}/λ_z, where C_{last} is the observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase; AUC_∞ will only be presented for patients with a reliable λ_z for Cycle 1, 2, and 4
$t_{1/2}$ and λ_z	$t_{1/2}$ is calculated by the program as $\ln2/\lambda_z$ for Cycles 1, 2, and 4; the terminal elimination rate constant (λ_z) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}.
CL and CL_{ss}	CL will be calculated by program as (dose/AUC_∞) for Cycle 1 and 2 (total and conjugated SYD985 only); For Cycle 4 CL_{ss} – Clearance at steady state will be calculated by program as (dose/AUC_{tau});
V_z and V_{ss}	V_z will be calculated by the program as (dose/AUC_∞)/λ_z (total and conjugated SYD985 only) for Cycle 1 and 2; V_{ss} for Cycle 4 will be calculated by program as (MRT_{inf}/CL_{ss}) where MRT_{inf} is mean residence time
RC_{max}, $RAUC_{tau}$ and $RAUC_{last}$	RC_{max}, $RAUC_{tau}$ and $RAUC_{last}$ will be calculated as ratios of the parameters for Cycle 2 vs. Cycle 1 and Cycle 4 vs. Cycle 1.

The following PK acceptance criteria will be applied to assess the reliability of elimination parameters:

• Number of points to calculate λz is greater than or equal to 3 excluding C_{max} point;
• Interval for calculation of λ_z is longer than half-life;
• The adjusted square of the correlation coefficient (Rsquare adjusted) for the goodness
  of fit of the regression line through the data points must be ≥0.85;
• AUCextrap% ≤30%.

10.3.5. PK Parameters Summarization

PK Summary Statistics

Variable	Summarized with:
AUC_{last}, AUC_{tau}, AUC_{inf}, AUC_{inf}/D, C_{max}, C_{max}/D, C_{min}, C_{last}, CL, CL_{ss}, V_z, V_{ss}, $t_{1/2}$, and λ_z	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
RC_{max}, $RAUC_{tau}$ and $RAUC_{last}$	n, arithmetic mean, SD, CV%, minimum, median, and maximum
T_{max}, T_{min} and T_{last}	n, minimum, median, and maximum

The following conventions will be used for the presentation of the descriptive statistics of PK parameters and of plasma concentrations:

PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits
Standard deviation	5 significant digits
CV and Geometric CV	1 decimal point

10.3.6. Statistical Methods

The relationship between randomization strata and demographic covariates (e.g. age, weight and randomization strata) and PK parameter for CL and CL_{ss} for total SYD985 only will be explored graphically using regression scatter plots.

11.   Pharmacodynamics

The Pharmacodynamic (PD) analysis is to be completed by Byondis. A listing of ctDNA and HER2 ECD sampling will be presented by treatment group, patient number and collection date and time.

12. Safety

The population used for safety analyses will be the Safety Analysis Set (SAS). Safety will be assessed on the basis of AE reports, clinical laboratory data, vital signs, ECG parameters, LVEF data, ophthalmological examination, ECOG performance scores, physical examinations and immunogenicity.

12.1. Adverse Events / Adverse Drug Reactions

AEs will be summarized by the SOC and PT based on the latest MedDRA dictionary.

The Common Terminology Criteria for Adverse Events (CTCAE) grades will be summarized by SOC and PT, using the National Cancer Institute (NCI) CTCAE version 4.03.

Only treatment-emergent adverse events (TEAE) will be summarized. TEAEs are AEs reported to start within the in-treatment period. The in-treatment period is defined as the period starting from the first dosing of study drug up to and including the treatment discontinuation visit. Events starting before first dosing will be listed.

SAP section 7.3 describes how to deal with partial or missing AE dates. If the relationship to SYD985 or any of the physician's choice treatments is missing then the relationship will be counted as related for the summary tables. Note related is defined as 'possibly' or 'probably'. Similarly, missing severity will be counted as Grade 3.

The summary tables will include the number of patients and the number of events. Percentages will be based on the number of patients. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum intensity, a patient will be counted once at the highest intensity level for which the event occurred at the SOC level and the highest intensity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level. The number of events will not be included in the maximum intensity summaries.

The summaries presenting frequency of AEs by SOC and PT will be ordered by descending frequency of SOC and then, within a SOC, by descending frequency of PT within the SYD985 treatment group.

Note for tables and listings: 'Conjunctivitis' will be recoded under the SOC 'Eye Disorder'. The original SOC of 'Infections and Infestations' will be kept in the ADaM.

The following AE tables will be provided:

- An overall summary of the number and percentage of patients reporting TEAEs, serious TEAEs, any treatment-related TEAEs (i.e. relationship to either SYD985, and/or lapatinib, and/or capecitabine, and/or trastuzumab, and/or vinorelbine and/or eribulin is 'possibly' or 'probably'. For the Physician's Choice group, if the drug relationship is related to one or to both of the drugs in the combination, the drug relationship is 'related'. An AE will be counted as 'Not related' only if the AE is not related to both of the drugs in the combination), TEAEs leading to any drug withdrawal (i.e. action taken is 'study drug permanently withdrawn'. For the Physician's Choice treatment group, two summaries will be provided: 1) TEAEs leading to withdrawal of both drugs; 2) TEAEs leading to withdrawal of one drug, TEAEs leading to death, AESIs, treatment-related serious TEAEs, treatment-related TEAEs leading to drug withdrawal (see above), treatment-

related TEAEs leading to death and treatment-related AESIs by treatment group. The 4 subgroups for Physician's Choice will be summarized separately. The table will be presented overall and by country.

- TEAEs overall and by SOC and PT by treatment group.
- TEAEs overall and by SOC and PT and by maximum severity, including a summary of Grade ≥ 3 by SOC and PT by treatment group.
- Serious TEAEs, overall and by SOC and PT by treatment group.
- TEAEs leading to discontinuation of study treatment, overall and by SOC and PT by treatment group. For the Physician's Choice treatment group, two summaries will be provided: 1) TEAEs leading to withdrawal of both drugs; 2) TEAEs leading to withdrawal of one drug.
- TEAEs leading to dose modification of study treatment (where action is 'dose delayed' or 'dose reduced'), overall and by SOC and PT by treatment group.
- Treatment-emergent AESIs, overall and by SOC and PT by treatment group. See section 12.1.1.
- Treatment-emergent AESIs by SOC and PT and by maximum severity, including a summary of Grade ≥ 3 by SOC and PT by treatment group. See section 12.1.1.
- Serious treatment-emergent AESIs, overall and by SOC and PT by treatment group. See section 12.1.1.
- TEAEs leading to death, overall and by SOC and PT by treatment group.
- Related TEAEs overall and by SOC and PT by treatment group.
- Related TEAEs overall and by SOC and PT and by maximum severity, including a summary of Grade ≥ 3 by SOC and PT by treatment group.
- Related serious TEAEs, overall and by SOC and PT by treatment group.
- Related TEAEs leading to discontinuation of study treatment, overall and by SOC and PT by treatment group. For the Physician's Choice treatment group, two summaries will be provided: 1) TEAEs leading to withdrawal of both drugs; 2) TEAEs leading to drug withdrawal of one drug.
- Related TEAEs leading to dose modification of study treatment (where action is 'dose delayed' or 'dose reduced'), overall and by SOC and PT by treatment group.
- Related treatment-emergent AESIs, overall and by SOC and PT by treatment group.
- Related treatment-emergent AESIs by SOC and PT and by maximum severity, including a summary of Grade ≥ 3 by SOC and PT by treatment group.
- Related serious treatment-emergent AESIs, overall and by SOC and PT by treatment group.
- Related TEAEs leading to death, overall and by SOC and PT by treatment group.

Only the TEAEs will be included in the summary tables, however all AEs will be included in the listings. Non-TEAEs will be flagged in the listings. Additional listings will be provided for deaths, SAEs, AEs leading to discontinuation of study treatment and AESIs.

12.1.1.   Adverse Events of Special Interest

The AESIs are defined in the protocol as:

- Interstitial Lung Disease/Pneumonitis
- Severe eye toxicity grade >=3
- Keratitis grade >=2
- LVEF decrease to <50%

Any AESI is flagged on the AE eCRF. These records will be selected and summarized as described above.

For ocular toxicity, in addition to summaries by SOC/PT, a Kaplan Meier table and figure with time (in weeks) to first episode of ocular toxicity (any grade) will be provided. Time is defined as the time from the start of the treatment to the first episode of ocular toxicity (any grade). If the patient does not have any ocular toxicity, censoring at the date of the patient was last assessed for adverse events.

Time to first ocular toxicity episode (weeks) = ([Date of first ocular toxicity episode – date of first dose] + 1) / 7

Time will be analyzed using Kaplan Meier quartile and 60 %, 70 %, 80 % and 90 % percentiles estimates along with 2-sided 95% CIs. Kaplan Meier plots will be provided and each treatment will be differentiated with a different line style.

The above analysis will be repeated for time (in weeks) to first episode of ocular toxicity grade >=2 and time (in weeks) to first episode of ocular toxicity grade >=3.

Additional Kaplan Meier tables and figures, as described above for ocular toxicity, will also be produced for time (in weeks) to the first episode of keratitis, time (in weeks) to the first episode of keratitis grade >=2 and time (in weeks) to first episode of keratitis grade >=3. The analysis will be repeated for conjunctivitis and dry eye.

The top three reported eye events (conjunctivitis, dry eye and keratitis) will be evaluated further. A summary table for each event will be provided detailing the number of events and the number of patients with an event overall and by grade 1, grade 2 and grade >=3. The number of patients with a fluctuation will be summarized. A fluctuation is a decrease in severity followed by an increase in severity. The duration of each event will be summarized overall (total) and by grade.

Event duration is derived as:

Event duration = ((AE end date - AE start date) + 1) / 7.
If event is ongoing the last of the 3 dates: 1) last visit date up to the EOT visit; 2) last AE start date (any AE); 3) last AE end date (any AE) will be selected.

The duration of no event will be determined by subtracting the total event duration from the patients AE assessment time:

No event duration = AE assessment time ((end of AE follow up – first dose date) + 1) – total event duration + 1

An event will be defined as recovered where an AE end date is not missing. Duration of recovery for each patient will be summarized and is the start date of the highest grade to the end date of the last AE (if the AE is ongoing, an end date is imputed as described above for event duration):

Recovery duration = sum of each event duration from the event with the highest grade to the last event.

Duration of an AE following a dose modification (delay or reduction) will also be determined per patient follows:

Duration following dose modification = sum of each event duration from the event after dose modification to the last event.
The total duration per patient with a dose modification vs. without a dose modification will be summarized overall and by grade.

The number of patients with a grade decrease, no grade change or grade increase will be summarized. The time (weeks) to an increase or decrease in grade following dose modification will be summarized by patient and is derived as follows:

Time = (AE start date – dose reduction/delay date) + 1 / 7.

A swimmers plot (SYD985 only) detailing event duration by grade for each patient will be produced for each of the three events. The x axis is time (weeks) and the y axis will be patient number. One lane will be produced for each patient and time starts at the first dose date and finishes at the end of AE follow up. Each event start and stop date will be plotted using study day. Each lane will be divided into the period of time with no event, grade 1, grade 2, grade 3 and grade 4.

A listing (SYD985 only) will be produced, with a sub-heading for each of the three events, detailing event start and stop times (and study day from first dose), SYD985 dose (mg/kg) at AE start and end, action taken, grade, seriousness, relatedness, medication given and outcome. Event duration, duration by grade, total duration, total duration by grade and event recovery will be listed separately. A similar listing of event duration and recovery will be produced following dose reduction/delay.

12.2.   Laboratory Evaluations

Blood and urine samples will be taken at screening and at the timepoints as indicated in the flowchart (see protocol 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 only be performed locally. The central data will be used for haematology, blood chemistry and cardiac troponin summaries and CTCAE grading. Both central and local lab data will be listed. The following parameters will be included:

Heamatology:	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 (alanine aminotransferase), AST (aspartate aminotransferase), total bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine kinase (CK), GGT (gamma glutamyl transpeptidase), glucose, inorganic phosphorus, LDH, magnesium, potassium, sodium, total protein, uric acid.
Cardiac biomarkers:	Cardiac troponin I (cTnI) or cardiac troponin T (cTnT).
Urinalysis:	Dipstick for bilirubin, glucose, haemoglobin, ketones, and protein (microscopy if more than one parameter is positive).

All summaries will be based on results in SI units and will be output in the order listed above. High/low classifications will be derived relative to the result and normal range in SI units where normal ranges

exist. The eCRF states that differential counts can be entered as 'Absolute' values OR 'Percentage' values. Percentage white blood cell (WBC) differential counts will be converted to absolute values. As each differential always adds up to 100%, the total WBC can be used to derive absolute values. For example, if a relative neutrophil value = 70% and the total WBC = 6.20 10^9/L, then the absolute neutrophil value = 4.34 10^9/L (0.7 x 6.20).

Toxicity grading following the NCI CTCAE grades version 4.03 will also be derived for laboratory variables where applicable (see tables below). Note, where gradings require investigator/clinical input, this will not be considered and only the numeric criteria will be used for the assignments. If this results in the criteria for more than one grade being met, the highest (worst) CTCAE grade will be assigned. For creatinine only, the criteria based on the upper limit of normal (ULN) will be used (changes compared to the baseline value will not be used), e.g. CTCAE defines Grade 1 as >ULN - 1.5 x ULN or >1 - 1.5 x baseline. Only the ULN – 1.5 x ULN criterion will be used (and not the baseline criterion).

The following parameters are gradable:

Parameter	NCI-CTCAE Term
Haemoglobin	Anemia
Haemoglobin	Haemoglobin increased
Lymphocytes	Lymphocyte count decreased
Neutrophils	Neutrophil count decreased
Platelets	Platelet count decreased
WBC	Leukocytosis
WBC	White blood cell decreased
Albumin	Albuminuria
ALP	Alkaline phosphatase increased
ALT	Alanine aminotransferase increased
AST	Aspartate aminotransferase increased
Total bilirubin (note that direct bilirubin appear on the eCRF but it is only the Total bilirubin that is gradable)	Blood bilirubin increased
Calcium (corrected for albumin)	Hypercalcemia
Calcium (corrected for albumin)	Hypocalcemia
Creatinine	Creatinine increased
GGT	GGT increased
Glucose	Hyperglycemia
Glucose	Hypoglycemia
Magnesium	Hypermagnesemia
Magnesium	Hypomagnesemia
Potassium	Hyperkalemia
Potassium	Hypokalemia
Sodium	Hypernatremia
Sodium	Hyponatremia

The following parameters will not be graded as there is no corresponding term in the NCI-CTCAE document:

Erythrocyte count
Haematocrit
MCV
Basophils
Eosinophils
Monocytes
Reticulocytes
MCHC
BUN
Chloride
Creatinine kinase
Inorganic phosphorous
LDH
Total protein
Uric acid
cTnI
cTnT

For haematology, blood chemistry and cardiac biomarker summary tables by visit and change from baseline to visit for each laboratory parameter will be provided. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Day 1 pre-dose. Summaries will include data from scheduled assessments only. If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 7.1). SAP section 7.4 describes visit windows.

Urinalysis parameters will be summarized by treatment group and listed in CRF order.

Shift tables for haematology and blood chemistry from baseline CTCAE toxicity for each visit and to the maximum grade on treatment for each parameter will be provided. Patients with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in the worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per patient then the highest grade will be summarized.

For non-CTCAE gradable tests, a shift table will be provided showing shifts relative to the normal ranges (supplied by the central laboratory). This summary of normal range category changes illustrates the number and percentage of patients who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the planned time normal range category and the worst-case on-therapy normal range category. The worst-case post-baseline row will be used to summarize the patients' overall worst-case normal range category change during the on-therapy period. The determination of the worst-case during the on-therapy period takes into account both planned and unscheduled assessments. Only laboratory tests which cannot be graded per CTCAE v4.03 specified criteria will be included. Patients with missing baseline value are to be assumed to have normal baseline value. Worst-case can be either High or Low. If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a patient was high at baseline and decreases to Low during

the time interval, then the patient is counted in the 'Decrease to Low' category. Likewise, if a patient was Low at baseline and increases to High during the time interval, then the patient is counted in the 'Increase to High' category. Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

All laboratory results in original and SI units will be included in data listings. Listings will be sorted by treatment group, patient number, assessment date and parameter (in the order listed above).

Pregnancy test data will be listed by treatment group, patient number and date.

12.3. Vital Signs

Systolic and diastolic blood pressure, heart rate, oral temperature and oxygen saturation will be measured at Screening, Day 1 of all cycles, Day 8 and 15 of Cycle 1 and 2 and the Treatment Discontinuation visit. Weight is to be measured at Screening, Day 1 of all cycles and the Treatment Discontinuation visit.

12.3.1. Vital Sign Values of Potential Clinical Importance

The Potential Clinical Importance (PCI) Ranges are given in the table below for blood pressure and heart rate results. The values outside these ranges will be flagged on the listings as either 'Low' or 'High' relative to the PCI ranges.

Vital Signs Parameter	PCI Range	Unit
Systolic Blood Pressure	< 85 (L) and >= 160 (H)	mmHg
Diastolic Blood Pressure	< 45 (L) and >= 100 (H)	mmHg
Heart Rate	< 40 (L) and > 110 (H)	bpm

The change from baseline values will be compared to the ranges in the tables below and be flagged on the listings if outside of these PCI ranges.

Vital Signs Parameter	PCI Range	Unit
Systolic Blood Pressure (Change from Baseline)	Increase ≥ 20 and ≥ 40	mmHg
	Decrease ≥ 20 and ≥ 40	
Diastolic Blood Pressure (Change from Baseline)	Increase ≥ 10 and ≥ 20	mmHg
	Decrease ≥ 10 and ≥ 20	
Heart Rate (Change from Baseline)	Increase ≥ 15 and ≥ 30	bpm

12.3.2. Summary of Changes in Heart Rate from Baseline

A summary of changes in heart rate comparing the baseline value to the worst-case post baseline value will be provided.

For heart rate, both an increase and decrease in value are of clinical concern. The worst-case post baseline summary is used to summarize the patients' overall worst-case shifts post baseline. The determination of the worst-case post baseline will take into account both planned and unscheduled assessments.

Patients with missing baseline value are to be assumed to have a normal baseline value. The percentages are based on the number of patients with heart rate data at the specified planned time.

The oncology standard categories of clinical concern are:

- Heart Rate (bpm): 'Decrease to <60', 'Increase to >100'

Worst-case can be either High (ie >100) or Low (ie <60). If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the "Decrease to <60" category and the "Increase to >100" category. If a patient was High at baseline and decreases to Low during the time interval, then the patient is counted in the 'Decrease to <60' category. Likewise, if a patient was Low at baseline and increases to High during the time interval, then the patient is counted in the 'Increase to >100' category.

Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

12.3.3.   Summary of Increases in Blood Pressure from Baseline

A summary of increases in blood pressure parameters comparing the baseline value to each planned time and to the worst-case post baseline value will be provided. The worst-case post baseline will be summarized separately from the by-visit summaries. These summaries apply to blood pressure parameters where increases in value are of clinical concern. The worst-case post baseline summary is used to summarize the patients' overall worst-case shifts post baseline. The determination of the worst-case post baseline takes into account both planned and unscheduled assessments.

Patients with missing baseline values are assumed to have baseline value below the lowest threshold. The percentages are based on the number of patients in the treatment group with data for the vital sign parameter at the specified planned time.

The oncology standard categories for Systolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (140-159)'

- 'Increase to Grade 3 (≥160)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), or Grade 3 (≥160).
The oncology standard categories for Diastolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (90-99)'
- 'Increase to Grade 3 (≥100)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), or Grade 3 (≥100).

Note: Whole numbers are expected for systolic and diastolic blood pressure in mmHg. For values with decimal places in the data the following cut-offs will be used for programming of the oncology standard categories. For systolic blood pressure: Any Increase to ≥120, Increase to ≥140-<160, and Increase to ≥160. For diastolic blood pressure: Any Increase to ≥80, Increase to ≥90-<100, and Increase to ≥100.

An increase is defined as an increase in grade (eg, for diastolic blood pressure, if a patient had Grade 1 hypertension [84 mmHg] at baseline and at week 4 had an increase to 85 mmHg [still Grade 1], this is NOT counted as an increase). However, if the patient had an increase to 101 mmHg (Grade 3) this is counted as an increase and the patient will be counted in the 'Any Grade Increase' and the 'Increase to Grade 3 (≥100)' categories).

Summary statistics for vital signs and weight at each scheduled timepoint and changes from baseline will be presented. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Day 1 pre-dose. Summaries will include data from scheduled assessments only. If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 7.1). SAP section 7.4 describes visit windows.

Note temperature will be reported in centigrade. Any conversions required will be as follows:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

Note weight will be reported in kg. Any conversions required will be as follows:

Weight (in kg) = weight (in lbs) * 0.4536

All vital signs and body weight will be provided in data listings. Listings will be sorted by treatment group, patient number, assessment date and parameter (in the order systolic blood pressure, diastolic blood pressure, heart rate, oral temperature and weight).

12.4. Central 12-lead ECG

Detailed ECG assessment will be described in a separate SAP. The SAP and any subsequent analysis will be completed by Byondis.

All ECG data collected in the eCRF will be provided in data listings. Listings will be sorted by treatment group, patient number, assessment date and timepoint for the SAS.

Any clinically significant findings will be reported on the medical history or AE page as applicable.

12.5.   Physical Examination

Clinically significant findings from the physical examinations will be reported as either medical history or AEs as applicable.

Physical examination data will be listed by treatment group, patient number and date of examination.

12.6.   Other Safety

12.6.1.   LVEF

LVEF assessments will be conducted at Screening, Cycle 2 Day 1, Cycle 4 Day 1 then every 4th cycle and at the Treatment Discontinuation Visit. Any clinically significant findings will be reported on the medical history or AE page as applicable.

A summary table of % LVEF by visit and change from baseline to visit will be provided. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Screening. Summaries will include data from scheduled assessments only. If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 7.1). SAP section 7.4 describes visit windows.

An additional table will be provided summarizing the dose modification categories for cardiotoxicity as described in protocol section 9.5.1.1. This table will also include a worst case post-baseline summary. The worst-case post baseline row is used to summarize the patients' overall worst-case shifts post baseline. The determination of the worst-case post baseline takes into account both planned and unscheduled assessments. Lower values represent the worst case, i.e. '<40' is the worst value; if a patient is within '40-<50' then '>=10' absolute decrease from baseline is worse.

LVEF data will be listed by treatment group, patient number and assessment date.

12.6.2.   Ophthalmological Examination

Ophthalmological examinations will be conducted at Screening, Cycle 2 Day 1, then on Day 1 of every 2nd cycle and at the Treatment Discontinuation Visit.

Ophthalmological examination results will be summarized for any clinically significant (CS) findings (i.e. if 'Yes' is selected for slit lamp exam and/or corneal sensitivity testing and/or pachymetry) overall and by visit. Time to first CS finding in months (date of first CS finding – date of first dose + 1 / 30.5) will be summarized overall and by visit. Slit lamp exam, corneal sensitivity testing and pachymetry tests will be summarized separately as described above for any CS findings.

Values by visit and change from baseline will be summarized for tear film break up time (TFBUT) and corneal thickness. Summaries will be presented for the mean of both eyes and each eye separately. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Screening. Summaries will include data from scheduled assessments only. If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 7.1). SAP section 7.4 describes visit windows. TFBUT time will also be summarized using the following categories: >10 sec, >5-10 sec, <5 sec for the mean of both eyes and each eye separately.

Any clinically significant findings will be reported on the medical history or AE page as applicable.

Ophthalmological examination data will be listed by treatment group, patient number and assessment date.

12.6.3.   ECOG

ECOG performance status assessments will be conducted at Screening, pre-dose on Day 1 of each cycle and the Treatment Discontinuation visit. A summary table will be provided with the number and percentage of patients with change from baseline, 'Improved', 'No Change' and 'Deteriorated', by visit by treatment group. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Day 1 pre-dose. Summaries will include data from scheduled assessments only. If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 7.1). SAP section 7.4 describes visit windows. A summary table will also be provided where ECOG is presented as a continuous variable. Values by visit and change from baseline will be included.

ECOG data will be listed by treatment group, patient number and assessment date.

12.6.4.   Analysis of Immunogenicity

Detailed ADA assessment will be described in a separate SAP. The SAP and any subsequent analysis will be completed by Byondis.

Blood samples for SYD985 antibodies are collected at pre-dose on Day 1 of each cycle and the Treatment Discontinuation visit for the SYD985 treatment group only. This data will be listed by patient number, visit and collection date and time for the SAS.

12.6.5.   Lung Review

An external vendor will complete a lung review (pneumonitis) by timepoint. This data will be listed by patient number and collection date for the SAS. Other variables may be listed depending on the data imported.

12.6.6.   COVID-19

The following analysis will be completed:

1. COVID-19 related protocol deviations, summary and listing. See section 6.6
2. Missing assessments and missing visits due to COVID-19. See section 7.3
3. Subjects impacted by COVID-19 related study/treatment discontinuations. See section 8.1
4. Baseline demographics for patients starting treatment before vs. during the COVID-19 pandemic. See section 8.2.

13. Interim Analyses

There are no formal interim analyses planned for this study. An interim assessment of OS will occur with no implications in terms of future study conduct when the primary PFS analysis will be performed (i.e. at least 256 PFS events have occurred, as assessed by central review, or at least 95% of patients have discontinued treatment and only after all patients have been enrolled).

14. Changes from Analysis Planned in Protocol

There are no changes from the planned analyses as described in the protocol.

15. Reference List

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993; 85: 365-376.

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The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group.

Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. FDA May 2007

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

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Sprangers MAG, Groenvold M, Arraras JI, et al. The European Organisation for Research and Treatment of Cancer: Breast Cancer Specific Quality of Life Questionnaire Module: First results from a three-country field study. *J. Clin. Oncol* 14:2756-2768, 1996.

16.   Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

Phoenix WinNonLin version 6.4 or higher (Pharsight Corporation, Mountain View, California, USA) will be being used to generate PK parameters.

16.1.   General Considerations

- One SAS program can create several outputs or a separate SAS program can be created for each output at statistical programmer's discretion.
- Each output will be stored in a separate file.
- Output files will be delivered in Word (rtf) format.
- Numbering of TLFs will follow ICH E3 guidance.

16.2.   Table, Listing, and Figure Format

16.2.1.   General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8 (or 9. To be determined prior to programming)
- The data displays for all TLFs will have a 1.5-inch blank binding margin on top of a landscape oriented page and a minimum 1-inch blank margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8 (or 9. To be determined prior to programming).
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no colour), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2.   Headers

- All output should have the following header at the top left of each page:
Byondis BV SYD985.002
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the corresponding TLF output).

- The date output was generated should appear along with the program name as a footer on each page.

16.2.3.   Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The title is centred. The analysis set will be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Full Analysis Set

16.2.4.   Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column. P-values will be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings will be SYD985 first, and then physician's choice. A total column will be included for the disposition and demographic summary tables.

16.2.5.   Body of the Data Display

16.2.5.1.   *General Conventions*

Data in columns of a table or listing should be formatted as follows:
- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

16.2.5.2.   *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

```
N            XX
Mean         XXX.X
Std Dev        X.XX
Median       XXX.X
Minimum      XXX
Maximum      XXX
```

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details of this will be in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the date the program was run and the listing source (i.e., 'Table Generation: ddmmmyyyy hh:mm Listing source: 16.x.y.z').

17.   Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in ███████ ████ Developing Statistical Programs SOP (█████).

███████████ Developing Statistical Programs SOP (█████), Conducting the Transfer of Biostatistical Deliverables SOP (█████) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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The TFL shells will be provided as a separate document.