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

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Version 2.0, dated 19 April 2023

Byondis B.V.

STATISTICAL ANALYSIS PLAN

PROTOCOL SYD985.003

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

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DOCUMENT HISTORY

VERSION HISTORY

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Version #	Chapter	Revision Summary	Reason(s) for Revision
1.0	N/A	Initial release	N/A
2.0	8.8.3	Added censoring rule for time to response	This is to complete the algorithm for time to response calculation
	8.8.4	Added subgroup analyses section	This is to analyze efficacy endpoints by subgroups
	8.9.4	Modified table design for vital signs reference ranges	This is to preset shift from baseline to any post-baseline values outside reference ranges
	8.9.7	Added on-treatment summary	This is to perform on-treatment analysis of worst-case ophthalmological results and time to event analysis

APPROVAL SIGNATURES

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

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	ALanine aminoTransferase
AP	Alkaline phosphatase
AST	ASpartate amino Transferase
ATC	Anatomical therapeutic chemical classification system
BUN	Blood urea nitrogen
CBR	Clinical Benefit Rate
CI	Confidence Interval
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DUBA	DUocarmycin hydroxyl Benzamide Azaindole
EAS	Efficacy Analysis Set
ECG	Electro Cardio Gram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transpeptidase

HER2	Human Epidermal growth factor Receptor 2
ICF	Informed Consent Form
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISH	In situ hybridization
LDH	Lactate DeHydrogenase
LVEF	Left Ventricular Ejection Fraction
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PFT	Pulmonary Function Test
PR	Partial response
Q3W	Dosing every three weeks
RECIST	Response Evaluation Criteria for Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SYD985	trastuzumab vc-*seco*-DUBA

TEAE	Treatment Emergent Adverse Event

2. INTRODUCTION

This statistical analysis plan (SAP) specifies the detailed procedures for performing the statistical analyses and producing tables, listings and figures in the study described in Byondis B.V. (formerly Synthon Biopharmaceuticals B.V.) Protocol SYD985.003. The version of the protocol at the time of preparation of this SAP is Version 3.0 dated 30 September 2020.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the objective response rate (ORR) of SYD985.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate SYD985 with respect to:

- Progression-free survival (PFS);
- Overall survival (OS);
- Safety.

3.3 OTHER OBJECTIVES

The other objectives of this study are as follows:

- To describe time to response;
- To describe duration of response;
- To describe the clinical benefit rate (CBR);
- To explore genomic profile/response relationships.

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

This is an open-label, single-arm study in patients with HER2-expressing recurrent, advanced or metastatic endometrial carcinoma. This is defined as a 1+, 2+ or 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridization (ISH). Inclusion of patients with HER2 1+/2+, ISH negative tumours will be limited to a maximum of 50% of the total sample size. Eligible patients for this study should have progressed on or after first line platinum-based chemotherapy. Patients who have had two or more lines of chemotherapy for advanced/metastatic disease are not eligible.

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

4.2 STUDY TREATMENT

SYD985 (Byondis B.V.*, The Netherlands*): [vic-]trastuzumab duocarmazine

Drug product vials contain 80 mg sterile lyophilized SYD985 which should be reconstituted prior to use with 8.0 mL sterile water for injection to yield a solution of 10 mg/mL. SYD985 drug product

vials should be stored at 2 to 8 °C until use.

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

5. SAMPLE SIZE AND POWER CALCULATION

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

6. ANALYSIS ENDPOINTS

6.1 PRIMARY ENDPOINT

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

6.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints are:

- PFS;
- OS;
- Safety.

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

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

The endpoints related to safety include:

- Incidence and severity of (serious) AEs;
- Number of patients with dose modifications due to AEs;
- Changes in vital signs and weight;
- Changes in laboratory parameters;
- Changes in LVEF and ECG and ophthalmological examinations;
- Changes in ECOG performance status.

6.3 OTHER ENDPOINTS

- To describe time to response;

- To describe duration of response;
- To describe the clinical benefit rate (CBR);
- To explore genomic profile/response relationships.

7. ANALYSIS POPULATIONS

7.1 SCREENED SET

The Screened Set (SS) will include all patients who signed the pre-screening HER2 testing-ICF. Note that this set includes pre-screening and screening failures. This population will be used for the presentation of patient disposition, and eligibility criteria.

7.2 FULL ANALYSIS SET

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

7.3 EFFICACY ANALYSIS SET

The efficacy analysis set (EAS) consists of a subset of the FAS patients who has a baseline and at least one post-baseline tumour evaluation assessment or discontinued prior to the first tumour assessment due to clinical progression. The EAS will be used for the efficacy analysis.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

The statistical analysis will be performed using the software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual patient data, and results of statistical analyses, will be presented in individual patient data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: mean, standard deviation, median, minimum, maximum and number of observations. Categorical data will be described using frequency and percentage. Shift tables will be provided, where appropriate. One additional decimal point will be used for mean, median, Q1, Q3, and two additional decimal points will be used for SD. Percentages will be rounded to one decimal place or more if most results are close to 0 or 100.

Analysis Datasets produced for analysis will follow CDISC ADaM standard IG 1.1. ADaM specifications in define.xml 2.1. CDISC compliance of datasets will be checked by Pinnacle 21 and full Pinnacle 21 reports will be produced.

Any changes in the planned statistical methods will be documented in the clinical study report (CSR).

Study results, including for disposition, demography and efficacy, will be presented in tables by HER2 status i.e. HER2 low, HER2 high and total. However, safety results will be presented for the overall group only.

The following international dictionaries will be used for medical coding:

- Medical History events: MedDRA (version 23.0 or later)
- Medications: WHO Drug Dictionary (WHODrug Enhanced version March 2017 or later)

- Adverse events: MedDRA (version 23.0 or later)
- Prior cancer related surgery (MedDRA Version 23.0 or later)
- Prior and concomitant procedures (MedDRA Version 23.0 or later)
- Prior cancer treatments (WHODrug Enhanced version March 2017 or later)

The following derived variables will be applied throughout the study:

- Adverse event duration (in days) will be calculated as:
    - ((<event end date> minus <event onset date>) + 1) in days
- The following algorithm will be used for the study day determination:
    - Day 1 = Day of first study drug administration (i.e., at Cycle 1 Day 1). The day before Day 1 is Day −1.
    - Prior to Day 1 the algorithm is (<visit/examination date> minus <date of first study drug administration >)
    - Day 1 and subsequent days = (<visit/examination date> minus <date of first study drug administration >) + 1.
- Age will not be calculated. The age collected by the investigator will be used for all analyses.
- Duration of exposure will be calculated as:
    - [(last dose date – first dose date) + 22] in days
    - [(last dose date – first dose date) + 22] / 7 in weeks
    - [(last dose date – first dose date) + 22] / 30.5 in months

Since the effect of SYD985 is expected to continue for up to 3 weeks after dosing, 21 days is added to the computation of duration of exposure. For subjects who discontinue due to death, duration of exposure will be calculated as: [(death date – first dose date) + 1] in days.

A similar approach will be used for duration in weeks and months.

The response according to RECIST 1.1 will be as reported in the CRF.

8.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Baseline is defined as the last available assessment prior to first dose intake (including unscheduled assessments), e.g., Cycle 1 Day 1 pre-dose.

No re-mapping of visits will be done for this study. All analyses will be based on actual scheduled visits. Unscheduled visits results will, however, be included in 'worst case' summaries.

Visit windows are defined as follows:

Planned Visit/ Assessment Day	Window (days) for the Planned Visit/Assessment
Day 1 (Cycle 2 and onwards)	±3
Day 8 (Cycle 1)	±1
Day 15 (Cycle 1)	±1
Follow-up (30 days after treatment discontinuation)	±7

For certain assessments there are the following specific windows:

- Haematology/chemistry on cycle 1 Day 1: day -5 to day 1
- Haematology/chemistry on cycle 2 (and onwards) Day 1: day -3 to day 1
- Pregnancy test on cycle 1 Day 1: day -5 to day 1

- Pregnancy test on cycle 2 (and onwards) Day 1: day -3 to day 1
- Ophthalmological examination on cycle x Day 1: day -7 to day 1
- LVEF on cycle x Day 1: day -7 to day 1

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

8.3 HANDLING OF MISSING DATA

No data imputation will be done for missing clinical outcomes. Patients whose clinical response is unknown or not reported will be treated as non-responders i.e. they will be included in the denominator when calculating the percentages for clinical outcomes.

Incomplete/partial adverse events and prior and concomitant medications dates will be replaced by derived variables and imputed where required using the following rules:

For start dates:

- If the day of the month is missing, it is imputed to be the 1st if not in the month of treatment. If in the month of treatment, the reference start date of treatment will be imputed.
- If both the day and month are missing, they are imputed to be 01 January if not in the year of treatment. If in the year of treatment, the reference start date of treatment will be imputed.
- Missing years will be left as missing.

For end dates:

- If the day of the month is missing, it is imputed to be the last day of the month (i.e., 28, 29, 30, or 31).
- If both the day and month are missing, they are imputed to be 31 December.
- Missing years will be left as missing.

8.4 PATIENT DISPOSITION

Enrollment and disposition data including primary reason for treatment and study discontinuation, number of patients completing study and number of patients in FAS and EAS will be presented for each patient in data listings, and summarized by frequency tables.

Inclusion and exclusion criteria violations and patient enrollment eligibility will be presented by patient in data listings.

8.5 PROTOCOL DEVIATIONS

Protocol deviations will be classified as major and minor deviations.

At the end of the study, the final project-level protocol deviation Log will be provided to the sponsor prior to the database lock. Upon the study end, the final project-level protocol deviation Log, as well as the list of subjects excluded from the analysis populations of interest (if applicable), is approved by the sponsor and filed in trial master file (TMF).

Major deviations will be summarized in a table while all deviations will be listed. A separate summary will be provided for major protocol deviations related to COVID-19 and a column will be present in the listing to indicate deviations related to COVID-19. The FAS population will be used.

8.6 IMPACT OF COVID-19 ANALYSIS

To estimate the impact of COVID-19 major protocol deviations related to COVID-19 will be

summarized and listed. COVID-19-related reasons for missing assessments and dose delays will be specified in the corresponding listings.

8.7 PATIENT CHARACTERISTICS

8.7.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Background and demographic characteristics of the FAS and EAS populations including age (years) at signing main ICF, height, weight, race, ethnicity, child-bearing potential status, smoking status. Percentages will be based on the number of patients with available observations in the FAS or EAS.

Demographic information will be presented in data listings sorted by HER2 status and patient number.

8.7.2 DISEASE CHARACTERISTICS

Tumour stage at initial diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, medical conditions (including diagnosis and extent of cancer at screening) histology classification, tumour grade, disease status, extent of disease, site of metastasis, Hormone Receptor status, time from diagnosis to study start, time from most recent recurrence/ progression to study start will be summarized by HER2 status using descriptive statistics or frequency tables, as appropriate. Summary of HER2 status will be presented for FAS. Percentages will be based on the number of patients with available observations in the FAS or EAS.

Disease Characteristics will be presented in data listings sorted by HER2 status and patient number.

8.7.3 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Previous or current diseases will be presented in data listings sorted by HER2 status and patient.

Medical history data will be summarized by HER2 status, system organ class (SOC), and preferred term (PT) using the FAS sorted by the frequency SOC and PT within the SOC.

8.7.4 PREVIOUS CANCER TREATMENT

Previous or current diseases as well as previous cancer treatments (including surgery and radiotherapy) will be presented in data listings sorted by HER2 status and patient.

8.7.5 PRIOR AND CONCOMITANT MEDICATION

All prior (ended before the first study treatment administration) and concomitant (started on or after study treatment administration or ongoing at study entry) medications will be listed for the FAS population. In addition, all concomitant medications will be summarized (by Anatomical Therapeutic Chemical [ATC] level 1 term and PT).

Where start and end dates are partially available, imputation will be done as outlined in section 8.3. If start and end dates are completely missing or classifications cannot be conclusively made based on the available information, such treatments will be classified as concomitant medications.

8.8 EFFICACY ENDPOINTS AND ANALYSIS

8.8.1 ANALYSIS OF PRIMARY ENDPOINT

8.8.1.1 OBJECTIVE RESPONSE RATE

The primary efficacy endpoint is the objective response rate (ORR) defined as best overall

response of CR or PR based on RECIST 1.1 guideline. The best overall response is the best response recorded from the start IMP treatment until 30 days after the last dose of study treatment. The best overall response is defined as the best response across all assessments. For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR. When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met, when SD is otherwise the best response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second assessment and does not meet the minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimal interval of 6 weeks.

ORR will be calculated, using the EAS, as the proportion of patients responding. The ORR will be based on calculated responses from investigator lesion assessments.

Analysis will be done for confirmed ORR and unconfirmed ORR. Confirmed ORR is defined as PR or CR that is confirmed in repeated assessment, while unconfirmed ORR is PR or CR that is measured only once (with no assessment at least 4 weeks later confirming the RECIST response).

Proportion of patients with ORR will be presented along with its exact 95% confidence interval (CI). Patients with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. A sensitivity analysis will be conducted using the FAS.

Individual target lesion measurements and overall response assessments will be listed by patient and assessment date. Best objective response per RECIST 1.1 will also be listed. Best percentage change in tumour burden for individual patients will be summarized by HER2 status and shown in waterfall plots and best percentage change in target lesions over time will be shown in a spider plot.

Tumour scans will be collected and stored by a central imaging laboratory. Central independent and blinded assessment of these scans may be initiated at a later point in time when deemed necessary. If this is the case the SAP will be amended to reflect this analysis. Information on tumour scans sent for central storage/evaluation will be listed sorted by patient number.

8.8.2 Analysis of Secondary Endpoints

Progression-free survival

Progression-free survival (PFS) is defined as the time (in months) from first day of IMP treatment to the date of first documented investigator-assessed disease progression according to RECIST 1.1 criteria or death due to any cause in the absence of progression (whichever occurs earlier).

Patients who have not progressed or died at study closure will be censored at the time of their last objective tumour assessment. If the patient does not have a documented date of progression or death or if death or progression is after two or more missed assessments, PFS will be censored at the date of the last adequate assessment. Also, patients will be censored at the assessment date with an outcome other than 'unevaluable' prior to the date when a new anti-cancer therapy is started.

If a patient has no post-baseline objective tumour assessment, the PFS will be censored at the first day of IMP treatment + 1 day.

Progression-free survival will be summarized for the EAS population and FAS as sensitivity

analysis by HER2 status. The following statistics will be displayed:

- The proportion of patients who are progression-free associated with its exact 95% CI.
- The median along with 25th and 75th percentile time to progression or death (months) will be determined by Kaplan-Meier method. Its 95% CI will be performed using the Brookmeyer-Crowley method. The associated survival curve will be displayed for the overall group.

Progression-free survival will be listed for the EAS by patient and HER2 status.

Time since discontinuation of treatment (last dose date +1) to progression date (for patients who discontinued treatment for another reason than progression) and first date of subsequent anticancer therapy will be summarized. Also, for patients who discontinued treatment for another reason than progression, the number of patients continuing into observation phase with at least one tumour assessment according to RECIST and the number of RECIST assessments will be summarized.

OVERALL SURVIVAL

Overall survival (OS) is defined as the time (in months) from first day of IMP treatment to death from any cause.

Patients who are alive or who are not known to have died at the time of the analysis will be censored at the last known date they were alive. Patients with no post-baseline information will be censored at the date of start IMP treatment plus 1 day.

Overall survival will be summarized for the FAS population by HER2 status and overall. The following statistics will be displayed:

- The proportion of patients who are alive at the end of study follow-up with its exact 95% CI.
- The median time to death will be determined by Kaplan-Meier method. Its 95% CI will be performed using the Brookmeyer-Crowley method. The associated survival curve will be displayed for the overall group.

Overall survival will be listed for the FAS by patient and HER2 status. Survival Follow-up data (Observation phase and long term follow-up), including reason for death, will be listed for the FAS.

8.8.3 ANALYSIS OF OTHER EFFICACY ENDPOINTS

Exploratory endpoints of this study include time to response, duration of response and CBR.

TIME TO RESPONSE

Time to response is the time between the date of first IMP intake until first documented investigator-assessed response (CR or PR) according to RECIST 1.1. Also, time to confirmed response will be the time between the date of first IMP intake until first confirmed investigator-assessed response (CR or PR) as defined as a second assessment at least 4 weeks after first assessment.

Patients who did not achieve a CR or PR will be censored at the date of last adequate tumour assessment.

If a patient has no post-baseline objective tumour assessment, time to response will be censored at the first day of IMP treatment + 1 day.

The time to response will be analysed using the EAS population. Summary statistics including mean, standard deviation, median, Q1, Q3, Min, Max and total the number of patients with a response will be presented. The median, 25th and 75th percentile time to response determined by Kaplan-Meier and its 95% CI using the Brookmeyer-Crowley method will also be presented.

DURATION OF RESPONSE

Duration of response applies to patients whose best overall response was CR or PR according to RECIST 1.1, the start date is the date of first documented response (CR or PR) and the end date is the date defined as first documented disease progression or death from any cause (whichever occurs first). Patients who missed more than one scheduled visit after first documented response will be censored on the date of last objective tumour assessment prior to the missing scheduled visit. If the patient does not have a documented date of progression or death or if death or progression is after two or more missed assessments, DOR will be censored at the date of the last adequate assessment.

As a sensitivity analysis duration of confirmed response will be conducted. Confirmed Duration will be defined as first confirmed response until the end date which will be defined as first documented disease progression or death from any cause (whichever occurs first).

Summary statistics including mean, standard deviation, median, Q1, Q3, Min, Max and total the number of patients with best overall response CR or PR (n) will be presented for this endpoint using the EAS population. The median, 25th and 75th percentile time to response determined by Kaplan-Meier and its 95% CI using the Brookmeyer-Crowley method will also be presented.

CLINICAL BENEFIT RATE

The CBR is defined as the percentage of patients with CR, PR, SD or non-CR/non-PD. CR, PR, SD and non-CR/non-PD are defined according to RECIST v1.1. CBR will be summarized using descriptive statistics. The confirmed CBR will be defined as the percentage of patients with CR, PR, SD or non-CR/non-PD. CR, PR, SD and non-CR/non-PD on at least two consecutive assessments where the second assessment is at least 4 weeks after first assessment

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 from the first dose date until a response of PD is first recorded + 1 day.

Note if a later SD or non-CR/non-PD follows ‘Not Evaluated’ it is assumed that SD continued.

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.

These assessments will be analysed based on the data observed in the EAS population and will be determined by investigator tumour assessment.

Using similar analysis as CBR the percent of patients with reduction in target lesions will be summarized.

GENOMIC PROFILE/RESPONSE EXPLORATION

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

Depending on the size and nature of available data, descriptive statistics (including correlation coefficients, where applicable) and models to explore underlying relationship between genomic profile and response to study treatment will be presented. Additional information on the analysis

methods and results will be provided in the CSR.

8.8.4 Subgroup Analyses

Subgroup analysis will be performed for the primary endpoint, secondary endpoints, time to response, duration of response and clinical benefit rate. These subgroup analyses will be based on the EAS for all endpoints except for the Overall survival. For Overall survival subgroup analysis will be performed on the FAS. The following subgroups will be assessed:

- patients with serous carcinoma
- patients with non-serous histology
- group 1 of histological subtype (includes patients with serous carcinoma, clear-cell carcinoma and carcinosarcoma)
- group 2 of histological subtype (includes patients with endometrioid carcinoma, mucinous carcinoma, squamous carcinoma, mixed carcinoma and other)

8.9 Safety Endpoints and Analysis

8.9.1 Exposure to Study Treatment

The extent of exposure will be summarized, including total cumulative dose, number of infusions, duration of exposure, dose intensity and treatment compliance.

Dose intensity is defined as the ratio of total cumulative dose to the duration of exposure in weeks. Treatment compliance is defined as the ratio of total actual dose administered to total dose planned.

In addition, the total number of patients who had any dose modification (including dose delay and dose reduction), the reason for dose modification (AE or other), and the number of dose modifications per patient (1, 2, ≥3) will be summarized. Patients with multiple dose modifications (dose delays or reductions) will be counted once per unique reason.

Dose delays and dose reductions will also be summarized separately and will be listed for FAS patients.

The total number of patients who had any infusion interruption (respectively, any infusion rate reduction), the reason (AE, other) and the number of infusion interruptions (respectively, infusion reductions) per patient (1, 2, ≥3) will be summarized. Patients with multiple infusion interruptions or infusion rate reductions will be counted once per unique reason.

Infusion interruptions or infusion rate reductions will be listed for FAS patients.

The duration of exposure will be computed as defined in section 8.1.

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

8.9.2 Adverse Events

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later and grouped by SOC and PT. AEs should be graded by the investigator according to CTCAE (version 5.0 or higher). Treatment-emergent AEs (TEAEs), defined as AEs that occurred on or after the first day of IMP treatment up to the follow-up visit 30 days after treatment discontinuation, will be summarized. Events that started before the in-treatment period will be listed separately.

Adverse events will be classified as treatment emergent based on available dates. Where dates are missing, imputation will be done according to rules in section 8.3. AEs with start and end dates completely missing will be classified as treatment emergent.

The relationship of an AE to study drug is recorded as unlikely related, possibly related, probably related, or not applicable. Missing relationship will be considered probably related.

For analysis purposes, 'related' AEs will be those reported as possibly related or probably related, or those for which the relationship is unknown. Events that occurred before the patient received study drug will be considered 'not applicable'.

Adverse events will be presented in data listings including patient ID, dates, study day of event, MedDRA SOC, PT, seriousness, CTCAE severity, drug adjustment, treatment taken, relationship to study drug, and outcome, SAEs, AEs leading to discontinuation, AESIs, and AEs leading to death.

An overview table (including only treatment-emergent AEs) will also be presented with the number (and percentage) of patients with:

- At least one AE
- At least one related AE
- CTCAE grade 3/4 AEs
- CTCAE grade 3/4 related AEs
- At least one SAE
- At least one related SAE
- At least one AE requiring treatment
- At least one related AE requiring treatment
- At least one AESI (AE of special interest)
- At least one related AESI
- AEs leading to dose modifications (i.e., dose reduced or dose delayed)
- Related AEs leading to dose modifications (i.e., dose reduced or dose delayed)
- AEs leading to infusion interrupted or infusion rate reduced
- Related AEs leading to infusion interrupted or infusion rate reduced
- AEs leading to study drug discontinuation
- Related AEs leading to study drug discontinuation
- AEs leading to death
- Related AEs leading to death

The number of events will also be included in this overview table. This table will be for the overall group only.

All treatment-emergent AEs and treatment-emergent AEs related to treatment will be summarized by frequency tables broken down by:

- SOC and PT.
- SOC, PT and worst CTCAE grade.
- SOC, PT and worst severity.
- SOC, PT and drug relationship (only for treatment-emergent AEs).

SAEs, TEAEs leading to dose modifications, dose reduction, dosing delayed, infusion rate reduction or infusion interruption, AESIs, TEAEs leading to study drug discontinuation, TEAEs leading to death and their 'related to study drug' versions will also be summarized by SOC and PT.

8.9.3 LABORATORY DATA

The laboratory tests for safety analyses comprise the following:

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

Laboratory values will be converted into SI units and the severity grade determined based on CTCAE v5.0.

Descriptive statistics for each laboratory analyte at each assessment time will be tabulated. The change from baseline will also be summarized.

An analysis of individual patient changes will be presented using shift tables showing the change from CTCAE grade/intensity at baseline to the worst CTCAE grade/intensity (including unscheduled assessments) during the study.

The laboratory parameters will be presented in data listings sorted by patient, study day, study time, and analyte. Out-of-range values will be flagged with h (high) or l (low).

In addition, a shift table for laboratory parameters summarizing shift from baseline reference values to worst post-baseline values (including unscheduled visits) will be presented.

Only planned laboratory test results will be summarized in tables, others will be listed. Pregnancy test results will only be listed.

8.9.4 VITAL SIGNS

Summary statistics by scheduled time point will be presented for each vital sign. The change from baseline will also be presented.

A shift table summarizing shift from baseline values to any post-baseline values outside reference ranges will be presented.

The vital signs marked reference ranges are:

- Diastolic blood pressure: < 45 mmHg or > 100 mmHg.
- Systolic blood pressure: < 85 mmHg or > 160 mmHg.
- Heart Rate: < 40 beats/min or > 110 beats/min.
- Temperature: < 36.0 degrees Celsius or > 38.5 degrees Celsius.
- Oxygen saturation: > 88%.
- Weight: > 110 kg or ± 10% from baseline weight or < 45 kg or ± 10% from baseline weight.

Vital sign assessments will be presented for each patient in a data listing.

8.9.5 ELECTROCARDIOGRAM (ECG) ANALYSIS

Standard ECG parameters (e.g. heart rate, PR, QRS, QT, Bazett QTc, and Fridericia QTc) will be summarized by scheduled visits. Also, the overall interpretation (Normal, Abnormal - not clinically significant, Abnormal - clinically significant, Not Evaluable) of the parameters will be summarized for the overall group by visit. Shift from baseline to worst post-baseline value will also be presented.

All ECG data will be listed.

8.9.6 LEFT VENTRICULAR EJECTION FRACTION (LVEF)

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

The number of patients who have a LVEF decline to below 50% with an absolute decrease from baseline ≥ 10% points, have a LVEF decline to below 40%, or develop Grade 3 left ventricular dysfunction will be summarized. Left ventricular dysfunction will be identified by AEs with the PTs ‘Left ventricular failure’ and ‘Left ventricular dysfunction’.

All LVEF results will be listed by patient and study day.

8.9.7 OPHTHALMOLOGICAL EXAMS

Results of the eye examinations, which will include a slit lamp exam, corneal sensitivity testing, fluorescence tear film break up time, and pachymetry, will be summarized by scheduled visits. Additionally, worst on-treatment results will be summarized by number and percentage. Time to first clinically significant findings will be summarized by means of descriptive statistics separately for each type of ophthalmology examination and overall.

The number of patients who develop Grade 3 (or higher) keratitis or Grade 3 conjunctivitis will be summarized.

All ophthalmological exams results will be listed by patient, and study day.

8.9.8 PHYSICAL EXAMINATION

Clinically significant results in physical examination will be summarized by scheduled visits. General physical examination assessments will be listed by patient, and study day.

8.9.9 PULMONARY FUNCTION TEST (PFT)

Clinically significant results in pulmonary function test will be summarized by scheduled visits. PFT assessments will be listed by patient, and study day.

8.9.10 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG performance status will be presented in a frequency table for the overall group by scheduled time point. In addition, shift from baseline at each planned visit and worst post-baseline result will be summarized for the overall group.

ECOG performance status will also be presented for each patient in a data listing.

9. INTERIM AND FINAL ANALYSIS

No formal interim analysis will be conducted for this study. The primary analysis will be performed when all patients have been enrolled in the main study for at least 6 months or have discontinued study participation (i.e. completed the last study visit due to disease progression or start of a new anticancer therapy, discontinued from the study or lost to follow-up). All data collected after this date will be summarized and added to the final study report, e.g. as an appendix.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The planned analyses as described in this SAP do not deviate from the description in the protocol of the analyses to be performed.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the *protocol number* will be presented. On the next line a *table/listing number* followed by the *title* of the table/listing and p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.

The list of tables, figures, and listings (TFLs) is given in section below. Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

12. LIST OF TABLES, FIGURES AND LISTINGS

Table 14.1.1.1 Summary of Patient Disposition – Enrollment: All Screened Patients
Table 14.1.1.2 Summary of Patient Disposition: FAS Population
Table 14.1.1.3.1 Summary of Major Protocol Deviations: FAS Population
Table 14.1.1.3.2 Summary of Major Protocol Deviations Related to COVID-19: FAS Population
Table 14.1.2.1 Summary of Demographic Variables: FAS Population
Table 14.1.2.2.1 Summary of Diagnosis and Extent of Cancer at Screening: FAS Population
Table 14.1.2.2.2 Summary of Diagnosis and Extent of Cancer at Screening: All Screened Patients with non-missing HER2 Status.
Table 14.1.2.3 Summary of HER2 Status: FAS Population
Table 14.1.2.4 Summary of Previous Tumor Treatments at Screening: FAS Population
Table 14.1.2.5 Summary of Endometrial Cancer Therapy Prior to Study: FAS Population
Table 14.1.3.1 Summary of Medical History: FAS Population
Table 14.1.4.1 Summary of Prior Medications: FAS Population
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Table 14.2.1.1 Summary of Objective Response Rate: EAS Population

Table 14.3.1.18 Summary of Patients Reporting Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term: FAS Population
Table 14.3.1.19 Summary of Patients Reporting Non-Serious Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term: FAS Population
Table 14.3.2.1 Summary of Treatment Exposure: FAS Population
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Table 14.3.3.1 Hematology: Summary of the Actual and Change from Baseline by Parameter and Timepoint: FAS Population
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Table 14.3.4.1 Vital Signs: Summary of the Actual and Change from Baseline by Parameter and Timepoint: FAS Population
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Table 14.3.5.1 ECG: Summary of the Actual and Change from Baseline by Parameter and Timepoint: FAS Population
Table 14.3.5.2 ECG: Evaluations of Parameters by Visit: FAS Population
Table 14.3.5.3 ECG: Worst Change from Baseline over the Study: FAS Population
Table 14.3.6.1 LVEF: Summary of the Actual and Change from Baseline by Timepoint: FAS Population
Table 14.3.6.2 LVEF: Summary of the Last and Lowest Available Ejection Fraction Measurements: FAS Population
Table 14.3.6.3 Summary of Subjects with LVEF Decline: FAS Population
Table 14.3.7.1 Summary of Ophthalmological Examination - Slit Lamp – Number of Clinically Significant Findings: FAS Population
Table 14.3.7.2 Summary of Ophthalmological Examination - Corneal Sensitivity, Fluorescence Tear Film Break Up Time and Pachymetry: FAS Population
Table 14.3.7.3 Summary of Ophthalmological Examination - Pachymetry: FAS Population
Table 14.3.7.4 Summary of Ophthalmological Examination: FAS Population
Table 14.3.7.5 Summary of Ophthalmological Examination, On-Treatment Period: FAS Population
Table 14.3.8.1 Summary of Clinically Significant Results in Physical Examination: FAS Population
Table 14.3.9.1 Summary of Clinically Significant Results in Pulmonary Function Test: FAS Population
Table 14.3.10.1 Summary of ECOG Performance Status: FAS Population
Table 14.3.10.2 Worst Change from Baseline in ECOG Performance over the Study: FAS Population
Listing 16.2.1.1 Patient Disposition: All Screened Patients
Listing 16.2.1.2 Enrollment Details: FAS Population
Listing 16.2.1.3 HER2 Status: All Screened Patients

13. REFERENCES

Brookmeyer R, Crowley J. A Confidence interval for the median survival time. Biometrics; 1982; 38: 29-41.

14. APPENDIX I. STUDY FLOWCHART – ASSESSMENTS AND PROCEDURES

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

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

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

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