20 July 2023
EMA/391838/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jivadco

International non-proprietary name: trastuzumab duocarmazine

Procedure No. EMEA/H/C/005654/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

2L+	Second line or later in the metastatic setting
3L+	Third line or later in the metastatic setting
ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADME	Absorption distribution metabolism excretion
AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
ALT	Alanine amino transferase
ASCO	American Society of Clinical Oncology
AST	Aspartate amino transferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BLA	Biologics license application
BMI	Body mass index
CAP	College of American Pathologists
CBR	Clinical Benefit Rate
CES	Carboxylesterase
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
Cmax	Maximum observed plasma concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
CV	Coefficient of VARIATION
DB03	DESTINY-Breast-03 trial
DAR	Drug-antibody ratio
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
DOR	Duration of response
DP	Drug product
DS	Drug substance
DUBA	Duocarmycin-hydroxybenzamide-azaindole
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
GGT	Gamma glutamyl transpeptidase
HER2+	Human epidermal growth factor receptor 2-positive
HR	Hormone receptor
HR	Hazard ratio
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonization
ICI	Immune checkpoint inhibitor
ICR	Independent central review
IgG	Immunoglobulin G

IHC Immunohistochemistry
ILD Interstitial lung disease
IND Investigational new drug
IMP Investigational medicinal product
IRR Infusion related reaction
ISH In situ hybridisation
ITT Intention to treat
IV Intravenous
KM Kaplan Meier
KO Knock out
LABC Locally advanced breast cancer
LC-MS/MS Liquid chromatography tandem mass spectrometry
LVEF Left ventricular ejection fraction
MBC Metastatic breast cancer
MedDRA Medical Dictionary for Regulatory Activities
MCBS Magnitude of clinical benefit scale
MHRA Medicines and Healthcare Products Regulatory Agency
MTD Maximum tolerated dose
NA Not applicable
NCI National Cancer Institute
NE Not estimable
OAT Organic anion transporter
OCT Organic cation transporter
ORR Objective response rate
OS Overall survival
ODWG Organ Dysfunction Working Group
PFS Progression-free survival
P-gp P-glycoprotein
PK Pharmacokinetic
PRO Patient-reported outcome
PT Preferred term
Q3W / Q6W Every 3 or 6 weeks
QTc/QTcF Corrected QT interval (by Friderica)
RDE Recommended dose for expansion
RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1
RP2D Recommended phase 2 dose
SAE Serious adverse event
SAS Safety analysis set
SD Standard deviation
SmPC Summary of product characteristics
SoC Standard of care
SOC System organ class
T-DM1 trastuzumab emtansine (Kadcyla)
T-DXd trastuzumab deruxtecan (Enhertu)
TEAE Treatment-emergent adverse event
ULN Upper limit of normal

1. CHMP Recommendations

Based on the review of the data on quality, safety and efficacy, the application for trastuzumab duocarmazine, as single agent, in the "treatment of adult patients with HER2 (Human Epidermal Growth Factor Receptor 2)-positive metastatic breast cancer. Patients should have either:

- progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease, or
- progression during or after trastuzumab emtansine treatment in the locally advanced or metastatic setting."

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation. The details of these major objections are provided in the List of Outstanding issues. In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding issues (redacted from this report).

1.1. Questions to be posed to additional experts

Not applicable

1.2. Inspection issues

1.2.1. GMP inspections

No GMP inspection is required.

1.2.2. GCP inspections

The applicant stated that all studies of trastuzumab duocarmazine were conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents.

The CHMP has requested a routine GCP inspection of the clinical study SYD985.002, including the inspections of two investigational sites [Bordeaux and Singapore] and the sponsor site [the Netherlands]. Despite some major findings at the Bordeaux's investigational sites, conclusions from the inspectors were that data were reliable enough to be considered in the context of a MAA. However, the inspection at the Singapore site was impaired by multiples administrative difficulties, and led to several critical findings, especially with regards to direct access to the electronic medical records of subjects. Due to important difficulties to access and control the study records, inspectors were of the opinion that these data could not be used in the context of a MAA. Moreover, when inspecting the Sponsor's site, it was found that 11 other sites did not give full access to their electronic source data to the sponsor, but relied on paper documentation. These 12 investigational centres represented 17% of the study population, for which a very strong degree of uncertainty on the reliability of the data is identified. (**See major objection).**

1.3. New active substance status

Based on the review of available data on the active substance, the CHMP considers that the applicant sufficiently substantiated the claim that trastuzumab duocarmazine can be qualified as a new active substance in itself.

1.4. Additional data exclusivity /Marketing protection

Not applicable.

1.5. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Derogations from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for trastuzumab duocarmazine as single agent is for the treatment of adult patients with metastatic HER2+ breast cancer who have received for locally advanced or metastatic disease at least two HER2-targeting treatment regimens OR T-DM1.

2.1.2. Epidemiology

Breast cancer is the most commonly diagnosed female cancer and remains one of the leading causes of cancer death despite major advances in early diagnosis and treatment. Gene expression studies have identified several distinct breast cancer subtypes that differ significantly in prognosis as well as in the therapeutic targets present in the cancer cells. The current molecular classification for breast cancer includes the following subtypes: luminal A, luminal B, HER2-enriched, triple negative or basal, and normal-like breast cancer. Recently, the HER2-low subtype also appeared. HER2-enriched cancers are associated with aggressive tumour behaviour and poor outcome[1].

In Europe in 2020, breast cancer incidence was 12.1% of all cancers diagnosed, which is slightly higher than the worldwide incidence (11.7%). In the female population, breast cancer accounted for 24.5% of all cancers in Europe, whereas in men, the incidence falls below 3%. The worldwide 5-year prevalence of breast cancer was 15.4%, whereas in Europe it was 15.8%. Breast cancer is hence classified as the form of cancer with the highest prevalence both in Europe and worldwide[2]. In general, the estimated lifetime risk of being diagnosed with breast cancer is 1 in 7 (15%) for females in the European Union (EU)[3].

HER2-positive breast cancer represents approximately 15% to 20% of all breast cancers.

[1] Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes & Diseases. 2018;5 (2):77-106.

[2] 2020 I. International Agency for Research on Cancer. Cancer Today: Estimated number of new cases in 2020. Accessed on 03 May 2022. Available from: https://www.iarc.fr/[

[3] Commission E. Breast cancer burden in EU-27. 2020.

2.1.3. Biologic features

HER2 is a member of the HER family of receptor tyrosine kinases that also includes epidermal growth factor receptor (EGFR or HER1), HER3, and HER4. HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. In cancer cells, HER2 protein levels can be increased 10 to 100-fold above levels found in normal cells (Kraus 1987; Sliwkowski 1999).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmation by pathological assessment. Disease stage should be assessed according to the AJCC TNM staging system. HER2 testing should be carried out according to the American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) guidelines. HER2 is defined as positive by IHC (3+) when more than 10% of the cells harbour a complete membrane staining, and by ISH if the number of HER2 gene copies is ≥6, or the HER2/chromosome 17 (CEP17) ratio is ≥2 and HER2 copies ≥4, or HER2/CEP17 <2 and HER2 copies ≥6[4].

The signs of more advanced locoregional disease include axillary adenopathy (suggesting locoregional disease) or skin findings such as erythema, thickening, or dimpling of the overlying skin, suggesting inflammatory breast cancer. Symptoms of metastatic breast cancer depend on the organs involved, with the most common sites of involvement being the bone (e.g., back or leg pain), liver (abdominal pain, nausea, jaundice), and lungs (e.g., shortness of breath or cough).

HER2-positive metastatic breast cancer remains an incurable disease. Although treatment with anti-HER2 therapies has improved the disease outcomes for patients with unresectable or metastatic breast cancer, the disease invariably progresses. Once HER2+ breast cancer has metastasised, the estimated 5-year overall survival (OS) rate ranges from 15% to 26% (American Cancer Society 2018; National Cancer Institute 2018; National Cancer Institute (NCI)).

2.1.5. Management

Seven HER2-targeting therapies have been approved up to now in the EU for HER2+ breast cancer: 2 antibodies (trastuzumab and pertuzumab), 2 ADC (T-DM1 and T-DXd) and 3 small-molecule kinase inhibitors (lapatinib, neratinib and tucatinib).

Recommended first-line treatment for HER2+ unresectable or metastatic breast cancer (MBC) is trastuzumab + pertuzumab + taxane. For several years (before and during trastuzumab duocarmazine pivotal study conduction) T-DM1 was the gold standard second-line therapy based on consistent PFS and OS data from the EMILIA and TH3RESA studies. Recently, data from the DESTINY-Breast-03 trial (DB03) indicated that T-DXd is associated with a significantly improved PFS compared with T-DM1 (HR 0.28; p=7.810^22) in patients previously treated with trastuzumab and a taxane in the advanced disease setting. Based on DB03 results, an extension of indication was granted for T-DXd for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer from the second line setting (EMEA/H/C/005124/II/0014, 11/07/2022). T-DXd is now considered as the new standard of care at this stage where this drug is available, moving T-DM1 to a later-line setting or as treatment option . Tucatinib (Tukysa), in combination with trastuzumab and capecitabine, is often preferred as initial second line option for patients with brain metastases or progressing within 12 months after finishing adjuvant treatment with T-DM1 but is also used from the third line (Martinez-Saez and Prat, 2021). T-DXd and T-DM1 are a third-line treatment options for patients who have not received this agent in the second-line setting. In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in

[4] Wolff AC, Hammond MEH, Allison KH et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol 2018; 36(20): 2105–2122.

combinations (e.g. with capecitabine, trastuzumab or ET). Continued anti-HER2-based therapy is the current clinical standard for patients with HER2+ tumours. If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, trastuzumab beyond progression should be considered (ESMO Clinical Practice Guideline).

Unmet Medical Need in the Proposed Indication

Metastatic HER2+ breast cancer remains an incurable disease. Although treatment with anti-HER2-based regimens has improved the disease outcomes for patients with unresectable locally-advanced or metastatic HER2-positive breast cancer, the disease invariably progresses. Treatment of patients after progression on T-DM1/T-DXd remains a clinical challenge, and the prognosis of these patients remains poor. In the proposed indication, for the treatment of patients with metastatic HER2+ breast cancer who have received for locally advanced or metastatic disease at least two HER2-targeting treatment regimens OR T-DM1, Tucatinib + capecitabine + trastuzumab, T-DXd and T-DM1 appear to be the most active treatment options in the third-line setting and beyond (ESMO Clinical Practice Guideline). The choice of treatment depends on prior second-line therapy, patient characteristics (in particular brain metastases), toxicity profile and availability.

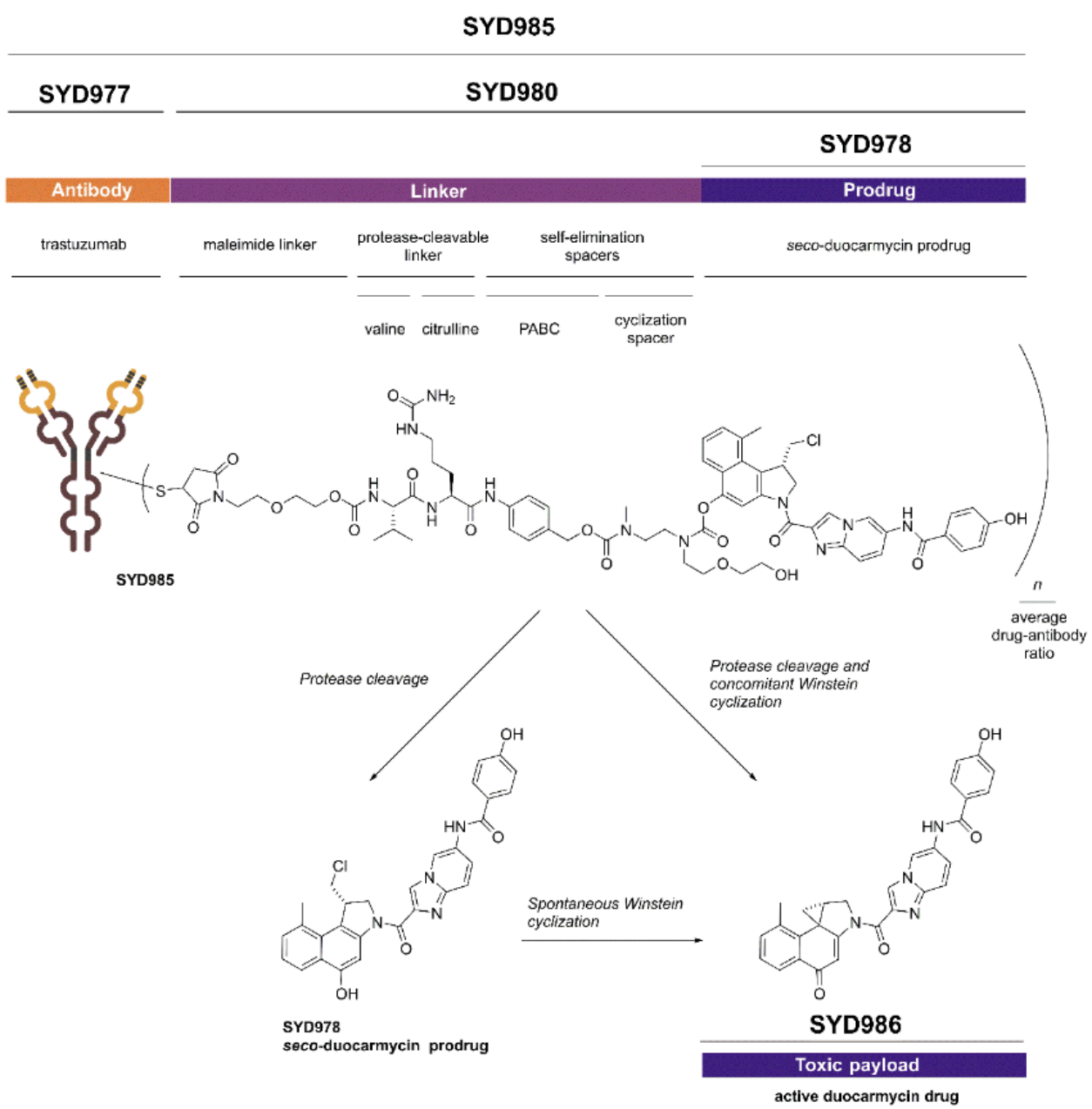
2.2. About the product

SYD985 is an antibody-drug conjugate (ADC) that belongs to the class of HER2 inhibitors.

SYD985 is an ADC comprising the humanised immunoglobulin G1 (IgG1) monoclonal antibody (mAb) trastuzumab (SYD977) covalently bound to a linker-drug SYD980. The ADC targets the human epidermal growth factor receptor 2 (HER2) via trastuzumab (similar to Herceptin) and delivers the toxic drug payload DUocarmycin-hydroxyBenzamide-Azaindole (DUBA) (SYD986), a DNA alkylating agent that damages DNA in both dividing and nondividing cells, leading to cell death.

After binding to HER2 on the cell membrane, SYD985 undergoes receptor-mediated internalisation and the linker is cleaved at the dipeptide valine-citrulline motif in the lysosome by proteases, such as cathepsin B. Subsequently, two self-elimination reactions occur to generate the prodrug (seco-DUBA, SYD978), which then spontaneously rearranges to form the active toxin (DUBA, SYD986). Alternatively, after linker cleavage, self-elimination and rearrangement may occur in a concerted process, in which SYD986 is directly formed. The active toxin (DUBA, SYD986) binds in the minor groove of DNA and alkylates adenine-N3 resulting in DNA damage and ultimately cell death in both dividing and non-dividing cells.

Figure 1: Schematic Representation of SYD985 and Mechanism of Release of Prodrug (SYD978) From SYD985



2.3. The development programme/compliance with guidance/scientific advice

The clinical development program for SYD985 commenced with the first-in-human phase I safety and efficacy trial denoted SYD985.001 (NCT02277717) comprising a total of 185 patients enrolled in Europe (Belgium, Netherlands, Spain and United Kingdom). According to the applicant, the results of SYD985.001 suggested that SYD985 was efficacious and had an acceptable safety profile in heavily pretreated patients with metastatic HER2-expressing solid tumours. In Part II of the phase I study expanded patient cohorts with specific HER2-expressing cancer types were evaluated. The observed objective response rate (ORR) indicated that SYD985 can be efficacious and safe for patients with advanced heavily pretreated HER2- expressing breast cancer, urothelial cancer, and endometrial cancer. Part II patients received SYD985 at the dose of 1.2 mg/kg (selected RP2D).

Evaluation of safety of SYD985 in the different cohorts did not raise any serious concerns for further development of SYD985 as a treatment for solid tumours.

Subsequently, SYD985 was evaluated in a comparative phase III trial in pre-treated HER2-positive locally advanced and metastatic breast cancer (SYD985.002/TULIP, NCT03262935) comprising patients from Europe, North America (USA/Canada) and Singapore, which is the pivotal trial supporting the indication in this initial license application. Trial SYD985.002 was designed as a randomised, active-controlled, superiority study in patients with pretreated 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 T-DM1 treatment for locally advanced or metastatic disease.

Subsequently, other trials were added to the SYD985 development program to explore other indications and combinations. Available safety data from 2 ongoing trials (SYD985.003 in endometrial cancer) and SYD985.004 (combination of SYD985 with niraparib in solid tumours) are included in this application in support of the safety evaluation.

Scientific advice

The clinical development plan of trastuzumab duocarmazine in the claimed indication have been discussed with FDA and EMA. The table below provides an overview of the interactions that have taken place with individual European authorities (national scientific advice) and EMA (Scientific Advice Working Party), including advice pertaining to the design of the pivotal comparative phase III trial and confirmation of a PIP waiver.

Table 1: European interactions on clinical strategy and clinical trial design

Date	Type of interaction	Major topics	Reference (Module 1.2, Annex 5.14)
3Feb2016	Scientific Advice Danish Medicines Agency, DK	– Eligibility for conditional approval based on PFS of at least 5 months using open-label non-comparative trial data – Eligibility for PRIME pathway	Meeting minutes DKMA
18Feb2016	Scientific Advice MHRA, UK	– Eligibility for conditional approval based on PFS of at least 5 months using open-label non-comparative trial data – Eligibility for PRIME pathway	Meeting minutes MHRA
29Feb2016	Scientific Advice Medicines Evaluation Board, NL	– Eligibility for conditional approval based on PFS of at least 5 months using open-label non-comparative trial data – Eligibility for PRIME pathway	Meeting minutes MEB
21Jul2016	EMA – Scientific Advice Working Party	– Eligibility for conditional approval based on PFS of at least 5 months using open-label non-comparative trial data – Sufficiency of single-pivotal comparative trial aiming to show increase in PFS compared to physician's choice to obtain MAA approval – Scientific feedback on design elements of pivotal efficacy and safety trial, including: - At least 35% increase in PFS as primary endpoint, OS as secondary endpoint - 2:1 randomization per pre-defined stratification factors - Physician's Choice (PC) reference treatment - Cross-over to SYD985 therapy following progression on PC - Central image analysis for primary endpoint - Quality of Life per EORTC QLQ-C30 and BR-23 questionnaires	EMA/CHMP/SAWP/469534/2016 Including a Scientific Advice Clarification letter, dated 05 October 2016

11Nov2016	EMA Human Medicines R&D Support Division	– Confirmation of PIP waiver	EMA/735157/2016
21Apr2017	EMA – Scientific Advice Working Party	– Follow-up advice on proposed comparative pivotal trial design: – PFS accepted as primary endpoint, OS as secondary endpoint, limitations and methodological considerations noted – Agreement to updated target indication and inherent change to inclusion criteria (related to early progression on prior T-DM1 treatment) – Proposed definition of HER2 positivity and central assessment considered adequate – Endorsement of proposed restricted choice of physician's choice treatment options – Agreement on proposed intensified assessment schedule for QTc effects	EMA/CHMP/232628/2017
		– Advise to assess QTc effects in both investigational arms and Physician's Choice reference arms – Agreement not to exclude patients based on QTc interval limits	
17Oct2019	EMA – Scientific Advice Working Party	– No further work to study metabolism, excretion and mass balance of SYD985 in humans, SYD985 as only metabolite to be quantified in humans – No need for dedicated drug-drug interaction studies with SYD985 and P-gp, BRCP and CYP3A4/5 – Proposal to use pop-PK to characterize the impact of organ dysfunction (i.e. no dedicated human renal or hepatic impairment studies)	EMA/CHMP/SAWP/544332/2019
16Oct20	NRG Communication	– (Conditional) Approval of invented name JIVADCO	201016 – EMA JIVADCO Approval EU

The scientific advice from the EMA related to the clinical development of trastuzumab duocarmazine and of key importance was acceptance of the proposed patient population and study design of SYD985.002, in particular the acceptance of the primary endpoint of PFS in this intended late line population and the choice of the treatment options in the standard arm. However, the applicant did not finally raise the OS secondary endpoint to the level of a key secondary endpoint, in deference of the SAWP advice given. SYD985.002 was globally deemed acceptable as confirmatory study, pending CHMP agreement after the assessment of data in the current application for a CMA.

A product specific waiver for the obligation to submit the results of studies with trastuzumab duocarmazine in all subsets of the paediatric population in malignant breast neoplasms was approved by the PDCO (EMA/735157/2016) and this is agreed.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

No GMP inspection is required.

GCP

The applicant stated that all studies of trastuzumab duocarmazine were conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents.

The CHMP has requested a routine GCP inspection of the clinical study SYD985.002, including the inspections of two investigational sites [Bordeaux and Singapore] and the sponsor site [the Netherlands]. The GCP inspection identified critical findings on the sponsor's lack of access to source data from 12 of the 78 clinical sites, representing 75 patients out of 473, leading to GCP uncompliant monitoring of these sites and potentially impairing data integrity (see point 1.2.2). The satisfactory responses to the inspection findings is an integral part of this procedure and will be needed by Day 181.

GLP

The studies have all been conducted in test facilities and sites that belong to national compliance programmes and had been inspected for their GLP compliance in the time of the conductance of the studies. One GLP major deviation in the management of the final report without any consequence on the scientific relevance of the study was identified. A minor deviation led to another concern concerning the homogeneity of the item tests SYD985 and SYD986. It has been discussed that the test item was homogeneous in repeated 4-cycle toxicity studies with SYD985 in cynomolgus monkeys due to similar Cmax values in animals exposed to the same dose. No difference in toxicity was observed when the concentrations were slightly different. The lack of impact of product homogeneity in some other studies was also discussed.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

Not applicable.

2.5.4. Conditional marketing authorisation

Not applicable.

2.5.5. Marketing authorisation under exceptional circumstances

Not applicable.

2.5.6. Biosimilarity

Not applicable.

2.5.7. Additional data exclusivity/ marketing protection

Not applicable.

2.5.8. New active substance status

The applicant provided additional data to support the fact that the active substance trastuzumab duocarmazine contained in the above medicinal product can be considered as a new active substance, as the applicant justified that it is not a constituent of a medicinal product previously authorised within the European Union.

2.5.9. Orphan designation

Not Applicable.

2.5.10. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.11. Derogations from orphan market exclusivity

Not applicable.

2.5.12. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0036/2018 on the granting of a (product-specific) waiver.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 80 mg of trastuzumab duocarmazine as active substance and proposed in clear glass vials sealed with a rubber stopper and cap.

3.1.2. Trastuzumab intermediate

3.1.2.1. General information

Trastuzumab drug intermediate (DI) is a humanised monoclonal IgG1 antibody against the ERBB2/HER2 receptor.

The active substance is expressed in CHO cells and contains two identical heavy chains (HC) and two identical light chains (LC). The heavy and light chains are connected by 16 disulfide bonds: 12 intra-chain disulfide bonds and 4 inter-chain disulfides bonds. SYD977 has an approximate molecular weight

of 148 kDa and has one N-linked glycosylation site located on the heavy chain at Asparagine 300 (Asn-300).

The features of the trastuzumab DI were appropriately addressed, further characterisation on the biological activity is presented.

3.1.2.2. Manufacture, process controls and characterisation

Manufacturers

The sites involved in the manufacturing of the trastuzumab antibody intermediate are provided. Valid GMP certificates have been provided for all sites, including the site performing mycoplasma and adventitious virus testing.

Description of manufacturing process and process controls

The manufacturing process is a standard monoclonal antibody manufacturing process. It consists of a cell culture process (upstream) and a protein purification process (downstream).

Acceptable ranges are provided for each process parameter alongside the parameter's designation as critical or noncritical. These include acceptable ranges for regeneration, sanitisation, and storage of chromatographic columns and UF/DF membrane used during the purification process. Justification of acceptable ranges is supported by a combination of process development and validation studies, manufacturing experience, and prior knowledge.

Information as regards IPCs and process hold times are provided. This is acceptable. Refer to the corresponding section for comments.

In general, the manufacturing process steps are adequately described.

Information as regards resin use cycles established during process validation are provided.

The surface areas for the virus and UF/DF filters are specified in 3.2.S.2.2.

Reprocessing in case of defined technical failures is detailed adequately.

Control of materials

A list of raw materials used in the manufacturing process, including filter and chromatography gels, is provided. Raw materials are tested according to European pharmacopoeia (where available), or according to in-house monographs. Animal derived materials used in the manufacturing process are discussed.

The composition of cell culture media and buffers is indicated.

Source, history and generation of cell substrate was adequately described. Supporting evidence of monoclonality has been provided. Cell banking system, characterisation and testing was adequately described. Descriptions of the adventitious agents test methods and results are provided.

Cell banking system, characterisation and testing

A two-tiered cell banking system consisting of a master cell bank (MCB)and working cell bank (WCB)was used. The banking procedure was adequately presented and characterisation performed in accordance with ICH Q5D guideline.

Control of critical steps and intermediates

In-process controls have been presented and acceptance criteria/action limits are provided. Most of the proposed IPCs relate to safety/microbial parameters (e.g. bioburden, endotoxins viruses). Cell culture is

also monitored by IPCs that evaluate process consistency (e.g. viability). Integrity testing of filters used in the antibody intermediate manufacturing process (e.g. nanofiltration, UF/DF, final formulation) are included.

Process validation

The approach to process evaluation was based on extensive process development studies, prior manufacturing experience and process risk assessments. In general, the Process Performance Qualification (and additional) data provided support that the process is well established and robust enough as to yield a consistent product.

Shipping of the antibody intermediate was not studied since the intermediate and drug substance are manufactured at the same location.

Manufacturing process development

The manufacturing process development is adequately described.

Characterisation

Elucidation of structure

The antibody intermediate has been thoroughly characterised. The predicted primary amino acid sequences of heavy chains and light chains have been verified. Post-translational modifications, glycosylation, charge and size heterogeneity, secondary structure and binding activity have been adequately investigated.

Impurities

Process- and product-related impurities were evaluated. Overall, the techniques applied for characterisation on trastuzumab intermediate are considered adequate and provide a complete characterisation of the molecule. The characterisation of impurities is considered adequate as well.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The specification for the antibody intermediate performed at release and during stability assessment includes control of identity, purity and impurities, potency and other general tests. Overall, the parameters included in the specifications are found to adequately control the quality of the antibody intermediate. Most acceptance criteria were found to be appropriate. Acceptance criteria for potency determination were under discussion at the time of withdrawal.

Analytical procedures

Most of characteristics of analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements. Validation of binding assay by ELISA was under discussion at the time of withdrawal.

Batch analysis

Batch data for trastuzumab intermediate were presented for batches used for pivotal clinical trials and other batches manufactured. All results have complied with the specifications approved at the time of release. The information is sufficient and acceptable.

Reference standards of materials

The history of the reference standards used throughout development of the trastuzumab intermediate, which were manufactured from trastuzumab intermediate lots representative of the respective development stage, is presented.
A two-tiered reference material approach is used.

Future PRM will be fully qualified by using a subset of relevant release methods of SYD977 DI, complemented by a panel of biochemical and biophysical characterisation methods. For qualification testing of a future SRS a similar approach will be followed.

Container closure system

The antibody intermediate is stored in bags. The choice of the container closure system has been justified and is in line with current pharmaceutical standards for biopharmaceutical manufacturing.

For stability studies, smaller bags are used and are constructed of identical materials. This is endorsed.

3.1.2.4. Stability

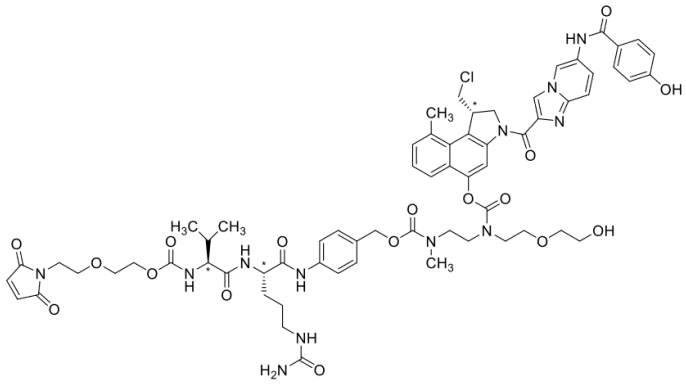
The applicant claims a shelf-life of 48 months for the antibody intermediate. This claim is based on stability studies that were carried out in accordance with ICH Q1A(R2) and Q5C. Accelerated and stressed stability studies were also conducted. A shelf-life of 48 months for the antibody intermediate could be granted. The applicant announced the intention to extend the shelf-life to a maximum of 60 months at the recommended storage condition. In addition, forced degradation studies applying several stress conditions (freeze/thaw, agitation, pH + temperature, oxidation and light) were performed.

3.1.3. Drug-Linker Intermediate SYD980

3.1.3.1. General Information

International non-proprietary name (INN):	Not applicable
United States Adopted Name (USAN):	
Chemical names:	4-((2S,5S)-13-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-5-isopropyl-4,7-dioxo-2-(3-ureidopropyl)-8,11-dioxa-3,6-diazatridecanamido)benzyl(2-(((((S)-1-(chloromethyl)-3-(6-(4-hydroxybenzamido)imidazo[1,2-α]pyridine-2-carbonyl)-9-methyl-2,3-dihydro-1H-benzo[e]indol-5-yl)oxy)carbonyl)(2-(2-hydroxyethoxy)ethyl)amino)ethyl)(methyl)carbamate
Other name:	
CAS registry number:	1345681-58-4
Laboratory code:	SYD980 vc-seco-DUBA (valine-citrulline-seco-duocarmycin-hydroxybenzamide-azaindole)
Molecular formula:	$C_{65}H_{75}ClN_{12}O_{17}$
Relative molecular mass:	1331.83 g/mol

Figure 2: Structural Formula



General properties

The information provided on general properties is rather limited. However, it can be regarded as sufficient for this intermediate. The important parameters such as solubility and polymorphism are sufficiently described.

3.1.3.2. Manufacture, process controls and characterisation

The sites involved in the manufacturing of the linker-drug intermediate are provided. Valid GMP certificates have been provided for all sites. A schematic overview of the manufacturing process is provided. The description of the manufacturing process and process controls is overall sufficiently detailed.

Relevant process parameters and amounts of materials, reagents and solvents are laid down in the process description with set points (no ranges are proposed). The set points appear to be justified by process development. The most significant process parameters are described.

In the light of the synthesis of the SYD980 moiety, the proposed starting materials seem to be rather advanced intermediates, with relatively few isolated intermediates separating them from SYD980. It is acknowledged that further steps of the manufacturing process of the drug substance SYD985 (conjugation, purification…) provide additional possibilities for purging the impurities. No question on the acceptability of the proposed starting materials as such is considered to be appropriate at this point. Information on the impact of impurities present in the starting materials on the impurity profile of SYD980 is provided. Some limits in the proposed starting materials specifications will be revised as more data is accumulated.

Suitable validation of the analytical methods used to control the quality of the starting materials should be confirmed (cfr. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities) – questions and answers).

The manufacturing process consists of a convergent synthesis whose longest branch comprises 7 chemical transformations. Nevertheless, the control strategy is complemented by a vast battery of in-process controls aimed at verifying reaction progression or monitoring of critical impurities. This is considered overall sufficient for an intermediate of the final drug substance, i.e. antibody-drug conjugate SYD985.

The process was overall adequately developed.

The data provided confirm the structure of SYD980.

The discussion about process impurities is generally acceptable since all starting materials & intermediates were considered as well as most of the expected by-products of the process.

Considering the advanced cancer indication, treatment of potentially mutagenic impurities as non-mutagenic is acceptable, in line with ICH M7.

Taking into account the conjugation step and extensive purifications taking place after conjugation, residual solvents and elemental impurities in intermediate SYD980 are not considered of concern.

3.1.3.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications include the most relevant parameters for the control of SYD980 and are roughly in line with ICH Q6A (although SYD980 is an intermediate and not the final active substance).

The analytical procedures are adequately described and validated; they include system suitability testing.

Batch analysis results confirm consistency & uniformity of the product. This is an indication that the process is under control.

Reference standards of materials

A Primary Reference Material (PRM) of SYD980 drug intermediate and a working standard have been prepared in-house. The working standard has been qualified against the PRM. The comparison of the IR spectrum of the PRM and the working standard is presented. The impurity reference materials have been purchased from commercial sources or prepared in-house.

Container closure system

SYD980 drug intermediate is packed under an inert atmosphere in glass bottles. The bottles are subsequently packed into a low-density polyethylene (LDPE) bag and finally into a laminated aluminium/LDPE bag. Given the photolability of SYD980, the tertiary packaging (ALU-LDPE bag) ensures full protection from light.

3.1.3.4. Stability

There are no clear trends in the long term study results. However, there is a trend towards degradation (increase in unspecified impurities, oligomers and total impurities) under accelerated conditions and in the photo stability study. In conclusion the proposed re-test period of 36 months at the recommended storage condition is justified.

3.1.4. Active Substance

3.1.4.1. General Information

Trastuzumab duocarmazine (INN, also referred to SYD985) is an antibody-drug conjugate (ADC) composed of the humanised monoclonal IgG1 antibody SYD977 (trastuzumab) covalently bound to a restricted number of linker-drug (SYD980) moieties, containing a seco-duocarmycin derivative.

The antibody moiety (SYD977) of the SYD985 ADC binds to the extracellular domain of the ERBB2/HER2 receptor. Upon internalisation of SYD985, the linker-drug (SYD980) is cleaved within the cell by proteases, thereby releasing the highly potent DNA-alkylating agent DUBA (SYD986).

The features of the DS were appropriately addressed.

3.1.4.2. Manufacture, process controls and characterisation

Manufacturer

The sites involved in the manufacturing of the trastuzumab antibody intermediate are provided. Valid GMP certificates have been provided for all sites.

Description of manufacturing process and process controls

The process consists of thawing of the trastuzumab antibody intermediate, followed by an ultrafiltration to prepare the subsequent reaction steps. The interchain disulfide bonds of the antibody are partly reduced and then, the SYD980 intermediate is added for conjugation. The antibody free thiols react with the maleimide functional group of the linker-drug intermediate to form the antibody-drug conjugate. Thereafter, unconjugated SYD890 and related impurities are removed by carbon filtration, then by means of a hydrophobic interaction chromatography (HIC). An ultrafiltration/diafiltration step is applied to concentrate and buffer-exchange the product and removes small molecules.

Finally, the recovered ultrafiltration and diafiltration pool is conditioned to the final concentration and composition of the drug substance.

In general, the manufacturing process is adequately described. However, based on the process validation data, as confirmed by the applicant, only two batches of each intermediate were pooled. Consequently, the description of the manufacturing process should be corrected in order to be consistent with the process validation data.

Information as regards IPCs and process hold times are provided.

The process parameters are defined for each manufacturing stage and are listed with PARs in the dossier.

The SYD985 DS manufacturing process makes full use of single–use materials and systems. The only exception is the product-dedicated multi-use Hydrophobic Interaction Chromatography (HIC) column. Resin lifetime studies were performed, as well as carry-over and resin lot-to-lot variation studies.

Control of materials

A list of raw materials used in the manufacturing process, including filter and chromatography gels, is provided. The solvent resistant prefilter used in stage 4 has been added. Raw materials are tested according to European pharmacopoeia (where available), or according to in-house monographs.

The composition of solutions and buffers is indicated.

Capacity of the process to remove raw materials is discussed.

Control of critical steps and intermediates

The IPCs defined for the control strategy are acceptable. Brief method details are provided for the IPC analytical methods.

In addition to IPCs, the applicant explains that the absence of KPIs in the proposed commercial control strategy is covered by the continued process verification (CPV) protocol. Based on the fact that limited batch data are available to date and that results for these KPIs have been provided for the process validation batches, the proposed approach is considered acceptable. In addition, the applicant states that, when further knowledge is gained, selected KPIs could become part of the commercial control strategy and that EMA will be informed.

Furthermore, it is stated that testing of buffers and process monitoring will take place during routine production. It is agreed that these parameters can be monitored as part of the CPV protocol. The

applicant intends to inform EMA when these parameters would remain important for proper control and would become part of the commercial control strategy.

Process validation

Validation of the drug substance manufacturing process was performed. Overall, the data showed that the selected quality attributes, key performance indicators, and in-process controls met their acceptance criteria when process parameters operated within their acceptable ranges.

The results of all CPP and non-CPP parameters are in line with the provided ranges, consistent and comparable. This is acceptable.

In follow up to PPQ and including re-assessed status of process parameters or IPCs, a Continued Process Verification (CPV) program was established. This approach is endorsed.

Information as regards transport validation is detailed and supportive data on temperature monitoring are provided.

Manufacturing process development

The manufacturing process development is adequately described.
Two manufacturing processes were mainly used during the process development history.
Several changes were introduced in order to scale-up the process and to increase robustness of the process.
Overall, it can be concluded that the pre- and post-change SYD985 DS batches are comparable.

Overall, the analytical data show that SYD985 DS material used in the pivotal (SYD985.002) clinical trial is not only comparable to the batches used for earlier (non-)clinical investigations, but also to the SYD985 DS material manufactured during PPQ.

Process characterisation studies were performed to develop the final commercial process.

The control strategy is adequately justified.

A risk assessment was carried out in which the contact materials and contact solutions used in the SYD985 manufacturing process were assessed for their potential to release extractables and leachables into the process solution ending up in the final drug substance.

In view of ICH Q3D guideline, a risk assessment on elemental impurities (EIs) was performed.
The risk of developing nitrosamine impurities in the SYD985 DS production process was assessed as low.

Characterisation

Elucidation of structure

Trastuzumab duocarmazine (SYD985 drug substance) has been thoroughly characterised. Intact mass, primary and secondary structure and protein conformation of SYD985 drug substance were confirmed.

Biological characterisation

The biological characterisation is found comprehensive and support the putative mechanism of action (MoA). The mechanism of action of SYD985 occurs via binding to HER2, which is overexpressed on the cell membrane of the target cell, followed by internalisation and cleavage of the linker drug on SYD985. This results in intracellular release of the active toxin, which subsequently alkylates the DNA and ultimately induces cell death.

Impurities

The characterisation of impurities is provided and considered adequate.

3.1.4.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The proposed active substance release specifications for the antibody drug conjugate (ADC) DS (SYD985) has been provided. The release specifications includes general tests, tests for identity, purity, tests for product-related substances and product-related impurities, test for process-related impurities, test for protein content, Potency by cytotoxicity and HER-2 binding as well as tests for safety.

Overall, the set of release parameters tested complies with ICH Q6B. Most acceptance criteria were found to be appropriate. Some acceptance criteria were under discussion at the time of withdrawal.

Analytical procedures

Most of characteristics of analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements. Validation of binding assay by ELISA was under discussion at the time of withdrawal.

Batch analysis

Batch analysis data of representative SYD985 DS batches are provided. The batches are manufactured at scale, using the intended commercial process.

Results confirm consistency and uniformity of the drug substance, indicating that the process is under control.

Reference standards or materials

The history of the reference standards used throughout development of the drug substance, which were manufactured from DS lots representative of the respective development stage, is presented.

A two-tiered reference material approach is used.

Future PRM will be fully qualified by using a subset of relevant release methods of SYD985 DS, complemented by a panel of biochemical and biophysical characterisation methods. For qualification testing of a future SRS a similar approach will be followed.

Container closure system

The drug substance is stored in bottles made of high-density polyethylene (HDPE). The choice of the container closure system has been justified and is in line with current pharmaceutical standards for biopharmaceutical manufacturing.

For stability studies, smaller bottles are used and are constructed of identical materials. This is endorsed.

3.1.4.4. Stability

The Company claims a shelf-life of 48 months for the drug substance. This claim is based on stability studies that were carried out in accordance with ICH Q1A(R2) and Q5C.

Accelerated (-20°C) and stressed (5°C) stability studies were also conducted.

In conclusion, a shelf-life of 48 months at -70°C and -40°C for the SYD985 DS could be granted.

The applicant states that "the shelf life of SYD985 DS will be extended to a maximum of 60 months at the recommended storage condition when supported by further real-time data." Any shelf-life extension will be submitted through a variation application procedure.

3.1.5. Finished Medicinal Product

3.1.5.1. Description of the product and Pharmaceutical Development

Description and composition of the product

The drug product (DP) is supplied as a lyophilised powder for concentrate for solution for infusion. Prior to use, the lyophilised drug product is reconstituted with Water for Injection (WFI). The reconstituted solution is a sterile solution which is then diluted in an infusion bag for dosing via intravenous infusion.

Pharmaceutical development

The drug product formulation evolved from a frozen formulation to a lyophilised formulation. The frozen formulation was used to supply the non-clinical studies and the phase I clinical trial. A comparability assessment was conducted between the frozen formulation and the lyophilised drug product. Manufacturing changes during development are described and comparability results have been provided.

Compatibility of the container closure system with the dosage form was demonstrated.

The microbiological quality complies with European requirements for sterile products and is ensured by a combination of various measures: process validation, manufacturing controls, in-process testing and release and stability testing.

The drug product is intended to be administered via intravenous infusion. Admixture compatibility and stability was demonstrated.

3.1.5.2. Manufacture of the product and process controls

Manufacturers

Trastuzumab duocarmazine finished product is manufactured and tested in accordance with EU GMP. The drug product manufacturing process consists of thawing of the drug substance, pooling and homogenizing, sterile filtration, lyophilisation, stoppering and capping.

Process validation

Validation of the drug product manufacturing process was performed.
The validation studies included the control of all process parameters (CPPs and non-CPPs) and IPCs, as well as critical quality attributes (CQAs). The results met acceptance criteria, demonstrating the drug product manufacturing process is consistent throughout the different steps (thawing, filtration, pooling, filling, and lyophilisation).

In follow up to PPQ, and including re-assessed status of process parameters or IPCs a Continued Process Verification (CPV) program is established.

The transport of the drug product is briefly described and sufficient supportive data are included.

Control of excipients

Formulation of the drug product does not include novel excipients and comply with the requirements and specifications of the relevant compendial monographs. No excipients of human and/or animal origin are present in SYD985 DP.

3.1.5.3. Product specification, analytical procedures, batch analysis

Specification

The drug product specifications were established in line with ICH Q6B.

The release specifications includes general tests, test for identity, purity and impurity tests for product-related impurities, process-related impurities test, drug-antibody ratio, test for protein and excipient content, Potency by cytotoxicity as well as tests for safety. Container closure integrity is tested for stability studies only. The proposed commercial acceptance criteria are valid at release and throughout the shelf life of SYD985 DP.

Most acceptance criteria were found to be appropriate. Some acceptance criteria were under discussion at the time of withdrawal.

Analytical procedures

Most of characteristics of analytical procedures (e.g. accuracy, precision, specificity, linearity, range, quantitation limit) were validated as per ICH Q2 requirements. Validation of the potency assay was under discussion at the time of withdrawal.

Batch analysis

Analytical results of drug product batches derived from process validation and clinical trials are provided. All batches were manufactured at scale. All results comply with the defined acceptance criteria.

Reference standards or materials

The reference standard used in the release of the drug product (DP) is the same as that used for the release of the drug substance (DS).

Container closure system

The primary container closure of trastuzumab duocarmazine finished product are clear glass vials sealed with a rubber stopper and cap. The container closure integrity has been adequately examined, and the sterilisation and depyrogenation for the container closure components has been validated as part of the process validation.

3.1.5.4. Stability of the product

A 48-month shelf life is proposed for trastuzumab duocarmazine finished product when stored at the recommended storage condition in the proposed container closure system, i.e. unopened vials. The stability studies are performed in accordance with current guidelines.

Stability studies were carried out in accordance with current ICH/CPMP guidelines. The containers used in the stability studies were the same as those proposed for routine storage.

The proposed shelf-life of 48 months at the recommended long-term (commercial) storage condition is deemed acceptable.

3.1.5.5. Adventitious agents

Materials of biological origin

All materials used in the generation of the cell line and in the manufacture of the SYD977 Drug Intermediate (DI) are animal-derived component free, except for the remote use of foetal bovine serum in the first cloning stage of the cell line generation.

Characterisation of cell banks in terms of virus safety

The cell banks were submitted to an extensive and appropriate panel of virus safety tests, as required by ICH Q5A and Q5D. The results were compliant: no adventitious agents were detected, and no endogenous retrovirus either, except for the expected presence of type A retrovirus-like particles. The results demonstrated appropriate quality of the cell banks in terms of microbiological, mycoplasma and endogenous and adventitious virus agents safety, and the results obtained with the CAL cell bank indicate that no new viruses are induced or introduced by the cell culture process conditions.

Unprocessed bulk harvest testing

An appropriate panel of virus safety tests is routinely carried out on the unprocessed bulk harvest, as release in-process testing, with a "None detected" acceptance criteria. The analytical methods are appropriately described and validated.

Viral clearance studies

The viral clearance studies are designed in compliance with the CPMP/BWP/268/95 guideline (selection of process steps to be evaluated, panel of tested viruses, scaled down process qualification, worst-case scenario). Two dedicated viral clearance and one contributing step show very effective virus reduction.

TSE issues

Considering that the sole material of biological origin (except for the CHO cell line) is the FBS (foetal bovine serum), which is used very remotely during cell line generation, the risk associated with TSE (transmissible spongiform encephalopathy) is deemed negligible.

3.1.6. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier presented in support of the Marketing Authorisation Application for Jivadco is of good quality. Information on development, manufacture and control of the intermediates, active substance and finished product have been presented in a satisfactory manner.

The viral safety of Jivadco is well addressed. The applicant provides a comprehensive overview of the strategy to minimise the risk of contamination by adventitious agents.

In conclusion, the applicant should satisfactorily answer the outstanding issues before the marketing authorisation can be granted.

3.2. Non-clinical aspects

3.2.1. Introduction

SYD985 is an antibody-drug conjugate (ADC) comprising the humanised IgG1 monoclonal antibody (mAb) trastuzumab (SYD977) covalently bound to a linker-drug SYD980. The ADC targets the human epidermal growth factor receptor 2 (HER2) via trastuzumab (similar to Herceptin) and delivers the toxic drug payload DUocarmycin-hydroxyBenzamide-Azaindole (DUBA) (SYD986), a deoxyribonucleic acid (DNA) alkylating agent that damages DNA in both dividing and non-dividing cells, leading to cell death.

The nonclinical program of toxicity studies for the ADC SYD985 is based on ICH guidance S9, the S9 Q&A supplement, and ICH S6(R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, with addendum, June 2011). In addition, considerations as described in ICH M3(R2) and ICH S7A and S7B guidances regarding safety pharmacology assessment have also been taken into account.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

SYD985 is an ADC composed of the humanised monoclonal antibody trastuzumab (similar to Herceptin) and vc-seco-DUBA, a cleavable linker duocarmycin payload.

The applicant has performed a large panel of in vitro studies to characterise the binding of SYD985 to its HER2 target and its subsequent desired effect (i.e. cytotoxicity). Based on the results presented, SYD985 appears to bind specifically to HER2 with an EC50 ranging from 0.15 to 0.54 µg/mL depending on the abundance of HER2 receptors on the cell surface. No Kd value was provided. EC50s have been calculated with different methods and in different experimental settings (e.g. ELISA). SYD985 demonstrated cytotoxicity against HER2 3+ 2+ but also 1+ lines with IC50s ranging from 6.9 to 114.9 ng/mL. Good conversion of the prodrug to SYD986 has been demonstrated. In in vitro studies, SYD985 was compared to T-DM1, these studies show that SYD985 is in general more potent than T-DM1.

Cell lines with a low concentration of HER2 require longer exposure to SYD985 and at a higher concentration compared to lines richer in HER2 receptors. HER2 receptors have been shown to be involved in SYD985-induced cell death, but there is also another unclear mechanism involved in cell death. SYD985 demonstrated ADCC activity similar to that of trastuzumab and also a by-stander effect. A study on the activity of metabolites found in vitro and in vivo in CES1c ko mice revealed that the genotoxic agent SYD986 and its prodrug had a cytotoxic potency 2000 times greater than other metabolites.

No data was provided showing the DNA binding and DNA-alkylating activity of the toxin DUBA (i.e. the mechanism of action of the DUBA-mediated cytotoxicity). A question was asked to the MAH in this regard. DUBA is a synthetic duocarmycin and there is literature data on the duocarmycin mode of action. Specifically, for SYD986 (DUBA), the applicant clarified that analytical studies have been conducted in which the nature of the DNA adduct of DUBA was investigated. DNA alkylation at the N3 position of adenine (N3 adenine adducts) was demonstrated following incubation of calf thymus DNA with SYD978 (prodrug) and SYD986 (DUBA). Furthermore, mechanistic studies confirmed that DNA adduct formation is important to the induction of cytotoxicity by SYD986. Altogether, the provided information supports the mechanism of action of the DUBA-mediated cytotoxicity.

SYD985 was shown to be unstable in mouse plasma due to the CES1c enzyme, but stable in human and monkey plasma. Cytotoxicity was observed at high doses, a sign of SYD986 release in humans and monkeys. Cathepsin is thought to be involved in ADC cleavage. The comparative binding data of SYD985 and SYD977 (trastuzumab) to human and cynomolgus monkey HER2, as assessed by surface plasmon resonance (SPR), indicates that SYD985 and SYD977 have lower affinity for cynomolgus monkey HER2 as compared to human HER2 (affinity of SYD985 for cynomolgus monkey HER2 is ±9-fold lower than for human HER2; affinity of SYD977 for cynomolgus monkey HER2 is ±10.8-fold lower than for human HER2). These differences in in vitro HER2 binding may not be readily translated to the antibody-target interaction in vivo. Moreover, such interspecies difference has been reported by others for trastuzumab.

SYD985 was shown to be able to induce cell killing of SK-BR-3 breast cancer cells via an ADCC-mediated mechanism and to a similar level as the naked mAb SYD977 (trastuzumab). However, both in section 6 of the pharmacology written summary and in section 5.1 of the SmPC, the ADCC-mediated cell killing is not mentioned as part of the mechanism of action for the antitumour activity of SYD985. The applicant was asked to discuss the contribution of ADCC-mediated cell killing activity to the mechanism of action of the antitumour activity of SYD985, and if relevant, to include the ADCC-mediated cell killing activity as part of the mechanism of action of the antitumour activity of SYD985 in section 5.1 of the SmPC. Moreover, it was also asked to add the bystander killing activity of SYD985 to the mechanism of action of the antitumour activity of SYD985 in section 5.1 of the SmPC. The SYD985 activity retains an intrinsic

ADCC activity. However, it will be used in patients who do not respond to trastuzumab-based treatment, which involves ADCC activity. In preclinical studies, SYD977 showed no efficacy in different breast cancer patient derived xenograft (PDX) models. The ADCC activity of SYD985 therefore does not contribute significantly to its antitumour activity. The justifications provided for not mentioning this activity as contributing to the efficacy of SYD985 are acceptable. The bystander killing activity was added in section 5.1 of the SmPC.

The activity of SYD985 has been studied in several in vivo experiments. The experiments include xenograft models of breast and lung cancer in CES1c KO mice. It demonstrated dose-dependent efficacy on lines with a high concentration of HER2 receptors but also on lines containing lower concentrations. SYD985 was compared to TDM in a lung cancer model whereas it would have been more interesting to compare the activity of the 2 ADCs in a breast cancer model given the indication of the scope of this Marketing Authorisation and since the TDM1 has shown its effectiveness in breast cancer.

In WT mice, it is likely that the activity of SYD985 is overestimated because it is rapidly cleaved by CES1c. It is conceivable that the WT models evaluate the activity of duocarmycin more than that of SYD985.

In conclusion, the in vitro and in vivo pharmacology studies support the use of SYD985 in the proposed indication (HER2-positive (score of 3 + by IHC or a ratio of ≥2.0 by ISH or by FISH) metastatic breast cancer).

3.2.2.2. Secondary pharmacodynamic studies

No data is provided which is acceptable under ICH S6/S9.

3.2.2.3. Safety pharmacology programme

Evaluation of the effect of SYD985 on the central nervous, cardiac and respiratory systems took place in repeated toxicity studies, which is acceptable when applying the ICH S9 guideline.

In vitro, SYD985 demonstrated 10% inhibition at 0.57 µM (280 ng/mL) of hERG channels. ±17,400-fold margin of exposure relative to the human Cmax of 16.1 pg/mL (geometric mean) for SYD986 at a clinical dose of 1.2 mg/kg/3 weeks

An increase in heart rate was observed with no change in ECG. In humans, an increase in heart rate has also been observed.

Regarding central nervous system damage, behavioural damage such as animal postures, decreased locomotor activity, tremors and aggressiveness were observed in monkeys treated with 10 mg/kg. Tremors and aggressive behaviour were also observed in the 3 mg/kg group. These effects could be due to an altered condition of the monkeys due to the toxicities of SYD985.

Regarding respiratory system, panting and transient laboured breathing were noted in a single female receiving 10 mg/kg. As this is 1 in 10 animals, it is not known whether it is directly linked to SYD985, in particular since at autopsy an adhesion of the heart (fibrotic adhesion of the epicardium of the ventricles attached to the pericardium) was noted and an effect on cardiovascular function in this animal may underlie the pulmonary effects and therefore be secondary. Given the uncertainties on the involvement of SYD985 in the respiratory effects observed and the low safety margins (<3) for the doses of 3 and 10 mg/kg, this effect cannot be excluded in humans.

3.2.2.4. Pharmacodynamic drug interactions

No studies provided.

3.2.3. Pharmacokinetics

For PK studies, *in vivo* and *in vitro* tests were carried out for the most part in the same species and strains as those used for the pharmacological and toxicology studies. Tests to verify the stability of the substances in the formulations before dosing have been carried out.

Immunoassays have been developed to measure antibody components as well as immunogenicity. The concentrations of ADC, Tab and ADA in mouse (Ces1c KO), rat and cynomolgus monkey plasma were determined by ELISA. LC-MS/MS assays were used to measure the circulating amounts of SYD978 and SYD 986 released from ADC. The assay for pharmacokinetic studies appears to be specific, sensitive, and linear over the specified concentration range. The analysis and validation methods are sufficiently discussed. Units of measurement are clearly defined. The methods have been validated for GLP studies and also for pharmacokinetic studies. There was a difficulty in assaying SYD985 and SYD986 in rats due to the rapid conversion of SYD985 to SYD986, several methods have been used to reduce this conversion without any real result. On the other hand, the assays in CESc1 KO mice and in monkeys are satisfactory.

The kinetics of SYD985 was evaluated in single dose and in repeated dose. The species used are mice, rats and monkeys. In mice and rats, due to the presence of the ADC-cleaving enzyme CES1c, exposure to SYD985 was low. This enzyme is absent in monkeys and humans. In CES1C KO mice, exposure to ADC was close to exposure to total Ab. Overall, exposure was proportional to dose in knockout mice and monkeys. In all studies, no gender differences were observed. The t½ was long and ranged from 93.5 to 171.7 hours for total SYD985 and 49.6 to 75.8 hours for conjugated SYD985. The half-life of SYD986 was similar to that of SYD985 conjugated, leaving assume that the concentrations of SYD986 are dependent on the concentrations of conjugated SYD985. SYD985 showed difficult distribution in blood cells. SYD978 showed instantaneous conversion to SYD986 when dosed IV in rats.

In monkeys, low exposure to SYD986 was observed (0.0071% to 0.0119% relative to SYD985). SYD986 also showed accumulation due to increased clearance of SYD985 in monkeys ADA positive (Cmax 15.6 and AUC 3.44 times higher).

The distribution of the product was determined by autoradiography on a Ces1c ko mouse. It revealed a strong distribution in blood, respiratory system (larynx and lungs), kidneys and liver. The exposure of the organs decreases slowly (75% of the radioactivity observable on D21). Weak passage of the BBB. SYD985 has a good affinity for tissues containing melanin such as the uveal tract and the skin. Phototoxicity studies conducted with SYD986 revealed no phototoxic potential, although radiation may aggravate skin toxicities.

Equilibrium dialysis, ultrafiltration, ultracentrifugation and the TRANSILXL method were used to determine plasma protein binding. The blood cell to plasma ratio is 0.864. The distribution in blood cells is slightly less than in plasma. The results suggest strong plasma protein binding.

Various methods have been used in the studies on the metabolism of SYD985 including autoradiography and LC-MS/MS. In the CES1c ko mouse, various metabolites were found in the plasma and faeces.

The kinetics of SYD986 was evaluated in CES1c knockout mice.

SYD985 was found to be unstable in mouse and rat plasma and stable in Ces1c KO mouse, monkey, human plasma and human blood. Main metabolites formed by hepatocytes were elucidated by RP-HPLC, autoradiography and LC-MS/MS.

No human-specific metabolites were detected. No data on human in vivo metabolism is available (radiolabelled human ADME study is considered not feasible by the applicant). In the EMA scientific advice EMEA/H/SA/3353/2/2019/II, there was a question (question 2) regarding ADME of SYD985 in humans. The CHMP considered the arguments to support a waiver for additional studies to characterise

the metabolism, excretion and mass balance of SYD985 in humans acceptable and agreed that SYD986 is the only metabolite that should be quantified in ongoing studies in humans.

An excretion balance study with 5 mg/kg radiolabelled [3H]-SYD985 dosed IV in female Ces1c KO mouse (study report NSR.PUK.59855) showed the main route of excretion was via faeces, with 60% of total radioactivity recovered and some excretion occurred via urine with 26% recovery. After dosing 0.09 mg/kg [3H]-SYD986 IV to female Ces1c KO mouse (study report NSR.PUK.59856), most excretion occurred via faeces (77%), with only a minor portion being excreted via urine (6%).

Modelling and simulation evaluated and integrated human SYD985 plasma concentration data obtained from clinical study SYD985.001 (data cutoff date is May 2017) and PK and tumour volume measurements from tumour growth experiments in Ces1c KO SCID mice. This translational PKPD modelling supports the selection of the 1.2 mg/kg Q3W dose regimen as the therapeutic dose in humans.

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

Several other non-GLP single-dose toxicity studies have also been conducted; see the table below for an overview of all the conducted single-dose toxicity studies:

Table 2: Overview of single dose toxicity studies

Type of Study	Species and Strain	Compound[a] and Method of Administration	Duration of Dosing or Exposure	Doses (mg/kg) or Concentration	GLP Com-pliant	Testing Facility	Study Report No.
Single Dose Toxicity							
DRF toxicity study	Mouse, C57BL/6 Ces1c KO	SYD985, IV injection	Single dose; 4 weeks postdose	50, 75, 100	N	WIL Research, 's-Hertogenbosch (NL)[b]	NSR.WIL.59940
DRF toxicity study	Rat, Wistar	**SYD978**, IV injection	Single dose; 2 weeks postdose	0, 0.09, 0.13, 0.18	N	WIL Research, 's-Hertogenbosch (NL)[b]	NSR.WIL.59937
Extended toxicity study	Rat, Wistar	**SYD978**, IV injection	Single dose; 1, 2 or 14 weeks postdose	0, 044, 0.089, 0.13	Y	WIL Research, 's-Hertogenbosch (NL)[b]	NSR.WIL.59923
DRF toxicity study	Rat, Wistar	SYD985, IV injection	Single dose; 4 weeks postdose	0, 10, 20, 30	N	WIL Research, 's-Hertogenbosch (NL)[b]	NSR.WIL.59939
Extended toxicity study	Rat, Wistar	SYD985, IV injection	Single dose; 1, 3 or 14 weeks postdose	0, 4, 8, 16	Y	WIL Research, 's-Hertogenbosch (NL)[b]	NSR.WIL.59938
1 or 2 dose toxicity study	Monkey, Cynomolgus	SYD982, SYD983, SYD984[c] IV slow bolus	1 or 2 cycles	0, 1, 3, 10, 30 [c]	N	CiToxLAB, Evreux (FR)[d]	NSR.CTX.59873

No DRF toxicity study with SYD985 was conducted in cynomolgus; however, non-GLP pilot study in female cynomolgus monkeys with SYD982, SYD983 or SYD984 by slow IV injection data are included in the dossier as they provided information regarding potential target organs and have been relevant for dose selection of the pivotal 4-cycle toxicity study in cynomolgus monkey. SYD982, SYD983, and SYD984 can be regarded as DAR average and distribution variants of SYD985 as they are composed of the identical anti-HER2 antibody SYD977 and linker-drug SYD980 randomly conjugated to endogenous thiols made accessible by controlled reduction, but their mean DAR differs. Moreover, SYD985 is prepared from SYD983 by an additional HIC purification, which reduces the amount of DAR 0 and DAR ≥6 species. At the dose levels of 1 and 3 mg/kg, the ADCs were given as a single IV bolus, and at 10 and 30 mg/kg, 2 dosing cycles were given at a 23- or 24-day interval, respectively. Terminal sacrifice occurred 7 weeks after the first dose. No drug-related preterminal sacrifices in moribund condition or deaths occurred in any group. No compound-related local reactions at the site of injection were noted. A reversible, slight to marked body weight loss was noted after each administration at the dose of 30 mg/kg with each ADC, but food consumption assessed qualitatively was not affected at any dose level. The target organs identified in this DRF study were skin, bone marrow, and mammary glands. Transient facial swelling of facial skin areas noted in individual animals showed no apparent relation to dose, had no relation to the induction of ADA, was not associated with deterioration in general condition, resolved without treatment, and did not occur upon a second administration. The induction of dose-related skin hyperpigmentation

noted by histopathology was regarded as adaptive and non-adverse. In bone marrow, a transient decrease of RBC generation (reticulocyte count) and peripheral blood WBC populations was noted, but only minimal to no suppression of platelet counts. Transient slight increases in AST and/or ALT were noted in individual animals at 30 mg/kg SYD982, SYD983, and SYD984 which were not accompanied by changes in other liver-related plasma parameters or histopathological changes. Hence, these are considered of questionable toxicological relevance. In mammary gland, minimal to slight non-adverse atrophy/involution of acinar cells in 1 of 3 animals at 30 mg/kg SYD982 and 3 of 3 animals at 30 mg/kg SYD984 and minimal focal squamous metaplasia of the acinar cells in 1 of 3 females at 30 mg/kg SYD984 were noted. As the maturity of the female animals used in this study was not established at the start of the study and histopathology of other reproductive organs was not performed, no conclusion regarding the adversity of these mammary gland findings could be made. The observation of slight cardiomyocyte hypertrophy in the absence of effects on relative heart weight in 1 of 3 females at 30 mg/kg SYD984 was reported as an equivocal finding.

The applicant conducted the pivotal single dose toxicity studies in Wistar rats, one with SYD978 which is the prodrug of duocarmazine, and SYD985 the antibody conjugate in development. For SYD978 the doses ranged from 0.044 to 0.133 mg/kg. For SYD985 the doses ranged from 4 to 16 mg/kg. The choice of doses is justified. Deaths were observed at the highest doses. Target organs identified are bone marrow, lymphoid organs, skin, eyes, uterus, intestines, and parotid glands with SYD985. Histopathological lesions of the heart, liver, kidneys, lymphoid organs, and lungs have also been observed with SYD978. Regarding the TK data, the exposure is generally proportional to the dose and no difference between the sexes was observed. However, the choice of Wistar rats for pivotal studies is not justified given the instability of SYD985 in rat plasma and the low affinity of SYD985 for its target in rats.

The applicant was asked to justify the choice of Wistar rats for these pivotal single dose toxicity studies and to discuss the role of SYD985 in the observed toxicities compared to SYD986 and also to elaborate on the safety profile of SYD985 in comparison with the known safety profile of trastuzumab and other trastuzumab-based ADCs. The toxicities targeted in the studies in rats relate to off-target effects, although the toxicities observed are considered to be partly linked to the ADC, since there is no complete deconjugation. This study also made it possible to highlight the differences in toxicities between rat and monkey, which would be linked to the increase in the concentration of the cytotoxic agent and/or PK differences linked to deconjugation in the rat. These justifications are acceptable. A comparison of the toxicological profiles of the 3 ADCs containing trastuzumab associated with a cytotoxic agent was carried out. Of the 3 ADCs, SYD985 is the most toxic and shows most target organs in monkeys (for example heart and spleen were only identified as target organs for SYD985). In the studies provided in the initial application, SYD985 demonstrated in vitro and in an in vivo study superior efficacy to T-DM1. Trastuzumab deruxtecan has fewer target organs than the two previous ADCs, but its antitumour activity is potentially less than SYD985 (to be confirmed in humans). According to the toxicology written summary (Module 2.6.6), 8 mg/kg is considered the highest non-lethal dose of SYD985 in the extended single dose intravenous toxicity and toxicokinetic study with SYD985 in Wistar rats (NSR.WIL.59938). However, there were preterminal sacrifices/deaths after a single IV dose of 8 mg/kg and the study report mentions that it remains uncertain whether 8 mg/kg should be regarded as a lethal or non-lethal dose level. The applicant was asked to discuss this discrepancy between the toxicology written summary and study report and the choice of 8mg/kg as the non-lethal dose level was correctly justified.

3.2.4.2. Repeat dose toxicity

The applicant performed a GLP repeat-dose toxicology study in sexually mature cynomolgus monkey (NSR.CLA.60346). Only one species was used in the pivotal repeat-dose toxicity studies with the ADC. This is acceptable (in line with ICH S9) as the antibody portion of the ADC seems to bind only to human

and NHP HER2 and not to rodent HER2. The cynomolgus monkey seems to be the only pharmacologically relevant species. In this study SYD985 was administered IV at 0/3/10/30 mg/kg once every 3 weeks for 10 weeks to 5 animals/sex/group (4 for control group) followed by a 8-week recovery period which is adequate to support Q3W dosing via IV infusion in adult advanced cancer patients. Different target organs were detected in repeated toxicity studies in monkeys. At a dose of 30 mg/kg, several deaths were observed and unplanned sacrifices were made. The main organs affected are the skin, the eyes, the striated muscles, the heart and the kidneys. Bone marrow damage with hypocellularity has been observed. Some of these damages were observed at a dose of 10 mg/kg (HNSTD), such as cardiac damage (degeneration of cardiomyocytes and inflammation), damage to the skin and eyes and also a reduction in white blood cells. At a dose of 3 mg/kg (MTED), skin lesions were observed. The toxicities observed are generally reversible and dose-dependent. These target organs were also found in single dose toxicity studies in rats. In that pilot study, the high dose level of 30 mg/kg was tolerated. In section 9 of the toxicology written summary (Module 2.6.6), plausible reasons are given for the difference in tolerability of the 30 mg/kg dose in the DRF study and the pivotal 4-cycle study in monkeys. The exposure margins for the doses of 3 and 10 mg/kg are low (refer to toxicokinetics data below), the toxicities observed can be found in humans, these toxicities are detailed below:

- Heart: Dose-related cardiomyocyte degeneration and subacute inflammation, correlating with increased cTnI levels, was observed in the monkey study. Following the recovery period, subacute inflammation was still noted but cardiomyocyte degeneration was not observed. In section 9 of the toxicology written summary (Module 2.6.6) it is mentioned that Onsum et al. (2013) have shown that HER2 expression is present in human atrial and ventricular tissue. Surprisingly, in the tissue cross reactivity study of SYD985 in human and cynomolgus monkey tissue panels (see section on other toxicity studies), there was no specific positive staining in the human and monkey heart tissue. In the TULIP clinical trial, LVEF decreased was reported in 3.8% of patients treated with Jivadco. In the SmPC, there is a warning for left ventricular dysfunction.

- Integumentary system

- Eye and lacrimal gland: In cynomolgus monkey, not all the effects on eye and lacrimal gland did fully reverse in the 8-week recovery period after the last dose. It is understood from section 9 of the toxicology written summary (Module 2.6.6), that also for several other ADCs, including T-DM1, there are nonclinical and clinical data that indicate eye and associated tissues to be a potential target organ. Ocular adverse reactions have also been noticed in humans treated with Jivadco; i.e. in 78% of the patients treated with Jivadco in the TULIP trial. In section 4.4 of the SmPC there are warnings and precautions for use regarding ocular adverse reactions. In the tissue cross reactivity study of SYD985 in human and cynomolgus monkey tissue panels (see section on other toxicity studies), there was specific positive staining in the human and monkey eye.

- Kidney: Dose-related non-reversible dose-related tubular effects were noted in this cynomolgus monkey study. At 3 mg/kg/cycle no effects on kidney were noted. At 10 mg/kg/cycle only minimal tubular cell hypertrophy was observed, but no remarkable changes in correlating renal safety biomarkers were noted. At the high dose (30 mg/kg), renal tubular degeneration associated with changes in clinical pathology/urinalysis and tubular hypertrophy were noted. In the animals that received 10 mg/kg and were allocated to the recovery period, the minimal tubular cell hypertrophy was still noted, indicating the 8 week period was insufficient to reverse the hypertrophy of the tubular cells. In the tissue cross reactivity study of SYD985 in human and cynomolgus monkey tissue panels, there was specific positive staining in the human and monkey kidney.

- Bone marrow, haematology and lymphoid organs: It is understood that myelosuppression is a well-known class toxicity of ADCs and also a hallmark of the duocarmycins.

- Skeletal muscle in tongue, larynx and oesophagus (only at high dose level): It is understood that his muscular tissue is not reported to have high levels of HER2 and that possibly, bystander toxicity from the HER2-expressing epithelia in this region or ADC catabolism by skeletal muscle as part of the general role of muscle in IgG catabolism are responsible for this effect. Plasma CK, in particular CK-MM iso-enzyme was shown to be a sensitive biomarker for the skeletal muscle effects.

ADAs that impacted the kinetics of SYD985 were detected in some monkeys, but the toxicities in ADA+ monkeys were broadly the same as those found in ADA - monkeys.

Non-GLP 3-cycle toxicity study of SYD985 in Ces1c KO mice:

The specific goals of this study were to evaluate the suitability of this special mouse strain for future mechanistic toxicology studies and, in particular, study the progress and spectrum of toxicity findings including effects on the eye and associated structures that have been observed in monkey and patients. Ces1c KO mice are relevant from a PK point of view but not from a PD point of view as SYD985 does not bind to mouse HER2. The toxicity profile determined in Ces1c KO mice is thus an off-target toxicity profile.

SYD985 (0, 5, 15 and 50 mg/kg) was given IV for three 3-week cycles to Ces1c male KO mice. No mortality occurred during the study. Three 3-week cycles of 50 mg/kg/cycle SYD985 induced alterations in testes, epididymides, skin (including injection site) and preputial gland, bone marrow, peripheral blood and spleen, pituitary gland, and liver. In addition, slight increases in ALT and AST (but no effect on ALP and bilirubin, no histopathological correlation) and changes in blood biochemistry likely indicative of loss of vascular integrity were noted. At 15 mg/kg, the slight increases in ALT and AST and the morphologic alterations in the preputial gland (acinar atrophy and increased severity ductal dilation) were also noted at lower severity. Moreover, several clinical signs mainly at the injection site and reduced body weight gain were seen at 15 mg/kg, and this dose level is considered to be the HNSTD for male Ces1c KO mice. Minimal to no test-item-related effects were observed at 5 mg/kg for three 3-week cycles. Ocular toxicity was not noted in the Ces1c KO mouse.

Apart from the skin effects, bone marrow suppression, and findings secondary to the latter effect (i.e., extramedullary haematopoiesis in spleen), the target organs affected were not very comparable to the toxicity profile observed in cynomolgus monkey. The additional target organs and tissues identified in male Ces1c KO mice were testes and epididymides, pituitary gland, preputial gland, liver, and an aggregate of effects indicating impaired vascular integrity. The effects noted at 15 and 50 mg/kg/cycle occurred at exposures that are substantially higher than the human exposures at the clinical dose (see Tables 16, 17 and 18 in toxicology written summary).

3.2.4.3. Genotoxicity

Three genotoxicity studies were conducted: a non-GLP Ames FTTM mutagenicity assay with SYD978, a GLP Ames assay with SYD986 and a non-GLP ToxTracker assay with duocarmycins (including SYD978, SYD986) and duocarmycin-related compounds.

The Ames GLP test was conducted on the different strains required (TA1535, TA1537, TA98 and TA100, WP2 uvrA). The concentrations of SYD986 were chosen according to the results of cytotoxicity studies, at logarithmic intervals. SYD986 was found to be stable for up to 6 hours in DMSO. The negative and positive controls gave results within the historical control data range. Based on the results obtained in the Ames assays (with and without metabolic activation) with SYD978 and SYD986 and in the ToxTracker assay, the toxic payload of Jivadco is considered genotoxic. The effect was dose related.

As the pivotal GLP-compliant Ames test with SYD986 is positive, it can be accepted (in line with ICH S9 and ICH S9 Q&A) that no further in vivo testing for genotoxicity is warranted.

3.2.4.4. Carcinogenicity

No study was submitted which is acceptable under ICH S9.

3.2.4.5. Reproductive and developmental toxicity

No specific fertility and early embryonic development study was conducted. This is considered acceptable in line with ICH S9. Information available from general toxicology studies on the pharmaceutical effect on reproductive organs was used as the basis of the assessment of impairment of fertility.

In the pivotal 4-cycle toxicity and PK study in cynomolgus monkeys, SYD985 (3, 10 and 30 mg/kg/cycle) was administered IV to sexually mature animals. Histopathological evaluation of male and female reproductive organs did not reveal any effects that would suggest an impairment of male or female fertility. In the male animals at 3 and 10 mg/kg/cycle there appeared to be (slightly) lower relative organ weights for the seminal vesicles, prostate and epididymides in particular at the end of recovery (Day 121) evaluation. These lower relative organ weights were not noted (to the same extent) at the end of dosing (Day 71). Relative testicular weights were lower on Day 71 for the 10 mg/kg group, and on Day 121 this parameter was lower for the 3 mg/kg group. The significance of these findings is very uncertain as no histopathological correlates were noted upon microscopic evaluation, and significant biological variation is rather common, even if sexually mature males were selected for this study. In 3 of 5 female animals at 30 mg/kg, minimal to slight hypertrophy of the glandular epithelium of the mammary gland was induced and the gland alveoli had enlarged, prominent nuclei with abundant cytoplasm. No effects on mammary gland were observed after four 3-week cycles of 3 and 10 mg/kg/cycle. The exposure margins between the NOAEL for effects on male and female reproductive organs in mature cynomolgus monkey (10 mg/kg/cycle) are 14.5 and 3.5 for plasma conjugated SYD985 and SYD986 AUCs, respectively. In section 5.3 of the SmPC, the results from the pivotal repeat-dose toxicity study in monkeys are described (no effects on reproductive organs that would suggest an impairment of male or female fertility at 3 and 10 mg/kg).

In the exploratory 3-cycle toxicity study of SYD985 (IV doses of 0, 5, 15 or 50 mg/kg/cycle) in male Ces1c KO mice, decrease in absolute testes weights was observed at 15 mg/kg/cycle and alterations in testis (flaccid and reduced testes size and weight, tubular degeneration/atrophy, Leydig cell hyperplasia), epididymides (reduced size and sperm content, luminal debris) and seminal vesicles (reduced weight) were observed at 50 mg/kg/cycle. The applicant considers the relevance of these findings in male reproductive organs in Ces1c KO mice for clinical effects on male fertility as uncertain as 50 mg/kg/cycle is associated with findings indicating a marked effect on vascular integrity, which may have contributed to a higher ADC penetration into organs including the male reproductive organs. How this compares to the actual exposure of male reproductive organs in the clinical setting is however not known.

The limited exposure ratios mainly based on dose levels (HED) at NOAELs in Ces1c KO mouse and monkey studies, the absence of formal fertility study, and the decrease in testes weight from the mid dose level in Ces1c KO mice were also taken into consideration to conclude that an effect on fertility cannot be excluded. In addition, it is a fact that the toxic payload SYD986 is a potent direct-acting mutagen. As such, an effect on male and female fertility cannot be excluded given the nature of the toxin being a DNA alkylating agent. This is clearly mentioned in section 4.6 and 5.3 of the SmPC. Moreover, section 4.6 includes advice for female and male patients to seek fertility counselling and advice on conserving eggs/embryos/sperm before starting treatment with Jivadco. This is fully supported.

Studies to evaluate effects on embryo-fetal development have not been conducted for SYD985. Considering that 1) NHP seems the only pharmacologically relevant non-clinical species for SYD985; 2) the toxic payload (SYD986) is genotoxic; 3) some associations with embryo-fetal developmental abnormalities were noted in human data on trastuzumab and 4) fetal exposure to the ADC and DNA

damaging payload is anticipated, the weight-of evidence indicates a risk for embryo-foetal development and embryo-foetal development studies are not warranted.

Section 4.6 of the SmPC describes the available human data on trastuzumab in pregnant woman and states that the cytotoxic component of Jivadco, DUBA, can be expected to cause embryo-foetal harm when administered to a pregnant women. The wording was adapted to reflect this conclusion. In addition, the level of recommendation in pregnant women in SmPC 4.6 was reinforced.

The contraception measures mentioned in SmPC section 4.6 are considered adequate. In view of the half-life of SYD985 and SYD986 in humans and the genotoxic potential of SYD986, the duration of the contraception measures for women of childbearing potential and men with female partners of childbearing potential following the last dose are considered adequate (in line with document 'Response from SWP to CMDh questions regarding genotoxicity and contraception' (EMA/CHMP/SWP/74077/2020)).

In accordance with ICH S9 and its Q&A addendum, prenatal and postnatal developmental toxicity studies are generally not warranted to support clinical trials or for marketing of pharmaceuticals for the treatment of patients with advanced cancer; hence, no studies were conducted.

The absence of juvenile toxicity studies is acceptable since the target population for treatment with Jivadco are adult patients.

3.2.4.6. Toxicokinetic data

In the pivotal 4-cycle toxicity study in cynomolgus monkeys with IV SYD985, the toxicokinetic data revealed no remarkable difference between the kinetics of SYD985 TAb and SYD985 ADC. No difference between males and females was noted. Exposure was generally proportional to dose. The exposure to SYD986 was very low, 0.0089% to 0.0158% compared to SYD985 and was more than proportional to the dose in the first days. SYD986 showed accumulation in ADA+ monkeys. Half-lives ranged from 66 to 170 hours for SYD985 TAb and from 29 to 160 hours for SYD985 AD. ADAs were observed in some monkeys which impacted the kinetics of SYD985 by reducing exposure to SYD985 and increasing that to SYD986. Analyses of plasma samples from control animals, as well as incurred sample reanalysis (ISR) was included.

3.2.4.7. Tolerance

No dedicated local tolerance studies have been conducted with SYD985. However, an assessment of local tolerability of SYD985 has been made in in vivo toxicity studies. The circumstances of IV infusion in monkey of SYD985 are most comparable to the administration procedure in humans. Based on the results from the macroscopic and microscopic examination of the IV injection sites in the pivotal 4-cycle toxicity study in cynomolgus monkeys, it can be concluded that SYD985 is well tolerated at the site of IV infusion (no changes observed that would suggest that the test item was irritating). It should be noted that effects on the tail at the site of injection were noted in several rats and Ces1c KO mice treated with either SYD985 or SYD978; hence, the intrinsic ability to induce local effects at the injection site is present for the payload and SYD985 under the conditions of IV bolus administration using the tail vein in rodent toxicity studies.

3.2.4.8. Other toxicity studies

No antigenicity studies have been conducted. ADA formation and its impact on PK and toxicity were assessed in repeated toxicity studies in monkeys. ADAs were formed in some monkeys, which were shown to be neutralizing. The decrease in exposure to Abs did not induce a remarkable difference in toxicities between ADA+ and ADA - monkeys, except for 2 ADA + monkeys in the 3mg/kg and 10mg/kg groups, in which the toxicities were less severe than monkeys ADA -.

No immunotoxicity studies were conducted because the immunotoxic effects observed in repeated toxicity studies were generally known class effects. Moreover, according to ICH S9 "For most anticancer pharmaceuticals, the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing". Immunotoxic effects observed in repeat toxicity studies were:

- Reversible suppression of WBC, RBC and PLT generation at ≥10 mg/kg/cycle

- Decreased germinal centres in lymphoid organs and thymic atrophy which led to preterminal sacrifice of monkeys at 30 mg/kg

A haemolysis study was conducted with SYD985 at final concentrations of 0.2, 1 and 5 mg/mL. SYD9895 demonstrated no haemolytic potential.

The phototoxicity of SYD986 was evaluated in vitro using the NRU Balb/c 3T3 test. SYD986 showed no phototoxicity.

In the TCR study, different human and monkey tissues were used. Generally, the staining was consistent between monkeys and human for epithelial tissues, making this an acceptable NC model for toxicity studies. However, staining was also observed in smooth muscle, blood vessels and connective tissue which was not observed in monkeys. It was also observed that non-specific staining was noted at the level of the bladder, the endothelium, the thymus and the spleen. Unexpected toxicities related to this binding can be observed on these organs.

Studies on metabolites: no additional studies to characterise the toxicity profile of certain metabolites are considered needed to support the marketing authorisation of Jivadco in advanced cancer patients. Based on in vitro metabolism studies, there were no unique human metabolites.

Studies on impurities: for the biological qualification of impurities, 2 toxicological studies are of importance: 1) the data of the extended single-dose toxicity and kinetic study with SYD978 in rat (NSR.WIL.59923; GLP study; see section on single dose toxicity) to provide the minimal toxic effect dose (MTED) as benchmark to relate the levels of unconjugated SYD980 and relate unconjugated duocarmycin-containing impurities to; 2) an in vitro cytotoxicity study in 3 cell lines (study NDR.NL03.85238; non-GLP) has been conducted in which SYD986 is compared to a number of duocarmycin-containing impurities (potentially) present as impurities in drug intermediate SYD980. Given the high potency of the duocarmycin payload used, a control strategy and limits for total unconjugated linker-drug-related impurities are in place. A limit for total unconjugated linker-drug-related impurities is proposed. This limit is supported by the extended single-dose toxicity study with SYD978 (seco-DUBA) in rat and by the comparative in vitro cytotoxicity study.

3.2.5. Ecotoxicity/environmental risk assessment

The ERA was performed for the active payload SYD986 of the ADC SYD985. This is considered acceptable as the antibody part of the ADC is unlikely to be a risk to the environment and the active payload SYD986 is the environmentally relevant chemical species.

PBT assessment

For the PBT assessment, only one experimental value of $\log D_{OW}$ is available: 3.24 at pH 7.4. The study was not conducted according to OECD 107 or OECD 123 under GLP. According to the ERA report this was due to two reasons:

- Firstly, SYD986 is highly toxic in its pure form, and therefore the amounts of test substance to be used in experimental studies should be kept as low as possible;

- Secondly, the solubility of SYD986 in water and octanol was very low, hampering the practical conduct of a $logK_{OW}$ determination as described in OECD 107 and 123.

As an alternative, an *in silico* log D prediction and a log D determination by a liquid-liquid distribution chromatography method at pH 7.4 were used. The value by QSAR calculations using MarvinSketch indicated a logP (=$logP_{OW}$) value of 2.52 for the non-ionic species. Since SYD986 is an ionisable substance, its octanol-water distribution coefficient should be considered at different pH levels, and the value at pH 7 is considered most realistic for PBT and chemical safety assessment. Marvin Sketch predictions show that the substance is present in its neutral form at a percentage of >80% in the pH range between 4 and 8, but will also co-exist in ionised form at these pH values. The *in silico* prediction of $logP_{OW}$ (2.52) for the neutral species is slightly lower than the experimentally derived logD at pH 7.4 (3.24) and the estimated logD at pH 7 (2.90).

Calculation of the predicted environmental concentration (PEC)

Regarding the calculation of the $PEC_{surfacewater}$:

a) The P_{region} is based on the crude incidence rate of breast cancer in females in Belgium in 2016 (i.e. country with the highest incidence rate in Europe). In the meantime, there are more recent (2020) crude incidence rate data available and for Belgium, the crude incidence rate of breast cancer in females has increased. In line with the answer to question 4 in the Q&A document (EMA/CHMP/SWP/44609/2010 Rev. 1), Fpen should be calculated for the member state with the highest prevalence of the disease and prevalence data should be as recent as possible, preferably not older than 5 years. The applicant was asked to take the most recent prevalence data for Belgium into account for the calculation of Pregion. The calculation of the refined Fpen (based on the prevalence of breast cancer) used for the calculation of the PECsw was requested to be reviewed to meet the requirements of the QA guidance document EMA/CHMP/SWP/44609/2016 (question 4).

b) Based on a worst-case approach, the refinement of the calculation of the $PEC_{surfacewater}$ by the % excretion of payload (25%) cannot be accepted. 100% excretion should be considered.

Applicability of the $PEC_{surfacewater}$ action limit of 0.01 µg/L

Concerning the applicability of the $PEC_{surfacewater}$ action limit of 0.01 µg/L, effects on fertility were evaluated based on the assessment of effects on reproductive organs in rat and cynomolgus monkey. A NOAEL was derived from the cynomolgus monkey toxicity study. In order to determine if there should be concern for effects on reproduction of fish and lower organisms following prescribed use of SYD985, the bioconcentration approach and the fish plasma model were considered. Despite the conservation of certain receptors and enzyme systems between mammalian and non-mammalian species, it can be stated that the distribution and number of these receptors are not equivalent, as well the response to the dose. On the other hand, it is difficult to establish a direct metabolic link between homeothermic and poikilothermic species. The applicant did not discuss and apply any safety margin due to interspecies variability and due to the quality of the information. It is not straightforward to transpose results from monkeys to fish. The best way to discard any effect on reproduction in fish is to perform an OECD test 229 (short term) and/or 234 (long term).

Generally, JIVADCO's ERA file (SYD985) was not considered admissible. Thus, different questions on the environmental risk had been raised. Data justifying the lack of solubility of SYD986 in water have been provided. Breast cancer incidence rate data have been updated to meet the requirements of the QA guidance document EMA/CHMP/SWP/44609/2016. The $PEC_{SURFACEWATER}$ of SYD986 was calculated with the corrected Fpen value. The calculation is acceptable. The MAH undertakes to provide an OECD117 study of the log kow and to adapt the ERA according to its results.

Summary of main study results

Substance (INN/Invented Name): trastuzumab duocarmazine/JIVADCO					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	4.63			Potential PBT (Y/N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.24			B/not B
	BCF	185.6			B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.85	pg/L			> 0.01 µg/L threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

3.2.6. Discussion and conclusion on non-clinical aspects

The non-clinical development of JIVADCO followed the ICH S9 and ICH S6 guidelines.

In vitro and *in vivo* pharmacology studies have demonstrated the activity of the product. However, several studies have been conducted in mice, they contain a CES1c enzyme which cleaves the ADC rapidly. These studies do not make it possible to conclude on the effectiveness of SYD985. Further studies in CES1c knockout mice have established the POC of SYD985 *in vivo*. It should be noted that SYD985 retains ADCC activity. It has also been compared to TDM1 (Trastuzumab Emtansine) in models other than breast cancer. No comparison can be made within the framework of this Marketing Authorisation, in fact, it would have been necessary to compare the activity of the 2 ADCs in breast cancer, given the indication of TDM1.

Regarding the pharmacokinetic studies, various methods were used (LC-MS/MS, HPLC, etc.) which made it possible to conclude on an exposure generally proportional to the dose, with no difference between the sexes. Autoradiography analysis following administration of radiolabelled SYD985 to Ces1c KO mouse confirmed the widespread distribution to blood and highly perfused organs as can be expected for an antibody-based therapeutic in a species that does not show target binding distribution. SYD985 has been shown to be rather stable in the plasma of humans, monkeys, and CES1c knockout mice. Neutralizing ADAs were observed in monkeys, but no significant impact on toxicities was observed. No major metabolites unique to humans were found. CYP cytochromes were involved in the metabolism of SYD986. The main route of elimination would be the faecal route.

The pivotal single-dose toxicity study with SYD985 was conducted in rats, which is surprising given the poor stability of the product in rat plasma. The GLP study in monkeys has revealed different target organs (heart; skin/integumentary system; eye and lacrimal glands; kidney; bone marrow, haematology and lymphoid organs; skeletal muscle in tongue, larynx and oesophagus). The effects were dose-dependent and generally reversible. Several deaths were observed at the dose of 30 mg/kg as well as sacrifices before the end of the study, which leaves a doubt as to the correct choice of the highest dose for this study. Phototoxicity studies have shown no phototoxic potential. However, given the toxicities observed on the skin, they may be exacerbated by exposure to UV radiation. The safety margins were low (≥ 3.5 based on HNSTD, and 0.6 based on MTED), under the scope of ICH S9, they are acceptable. SYD986 was found to be mutagenic in the Ames test. Results from the ToxTracker assay showed that the prodrug SYD978, a metabolite and reference duocarmycin SA were also potentially genotoxic. Other genotoxicity studies were not submitted.

Studies on environmental risk are not considered admissible. The Fpen and PECsurfacewater were re-calculated and the applicant initiated an additional study to experimentally determine the log Kow in accordance with OECD 117 at 3 environmentally relevant pH and that depending on the results further assessment might be required.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Data on the efficacy of SYD985 therapy in the claimed indication is primarily be based on the data of the 437 HER2+ metastatic breast cancer patients from the SYD985.002 trial (TULIP). The results from this trial constitute the basis of the application for the registration of SYD985. The information of Cohort A (HER2-positive metastatic breast cancer patients) of the first I human SYD985.001 trial will be used as supporting data.

Table 3: Overview clinical trials with SYD985 for the current registration

Trial ID	SYD985.001	SYD985.002 (TULIP)
IND #	*	131333
Phase	Phase I, FIH	Phase III
Countries	BE, NL, UK, ES	BE, NL, UK, ES, FR, IT, DK, SE, US, CA, SG
Trial title	A two-part first-in-human phase I trial (with expanded cohorts) with SYD985 to evaluate the safety, PK, and efficacy in patients with locally advanced or metastatic solid tumors	A multi-center, open-label, randomized trial to compare the efficacy and safety of SYD985 to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer
Trial Design	Open-label Part I: dose-escalation Part II: expanded cohorts	Open-label, randomized, active-controlled, superiority
Dosing regimen	Part I: 0.3 to 2.4 mg/kg Part II: 1.2 mg/kg IV infusions once every 3 weeks.	1.2 mg/kg SYD985 IV infusions once every 3 weeks
Trial population	Male or female Age ≥ 18 years Part I: locally advanced or metastatic solid tumors of any origin Part II: HER2-expressing breast, gastric, urothelial, or endometrial cancer	Female Age ≥ 18 years Histologically confirmed HER2-positive, unresectable locally advanced, or metastatic breast cancer
First Patient First Visit	30 Oct 2014	07 Dec 2017
(Planned) Enrolment	N=185	N=437 (N=291 SYD985 and N=146 physician's choice)
Patient Exposure	Total: 185 patients Part I: 39 patients Part II: 146 patients	288 patients dosed with SYD985, 137 patients dosed with physician's choice
Trial status	Completed	Ongoing for OS assessment
NCT	02277717	03262935

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Methods

The validations of the bioanalytical methods for (1) Total trastuzumab Fab antibody LTMB ELISA for the determination of total SYD985 concentrations; (2) conjugated antibody assay (coated anti-duocarmycin LTMB ELISA) method for the determination of conjugated SYD985 concentrations; (3) LC-MS/MS method for the determination of free SYD986 concentrations; and (4) AlphaLisa Immunogenicity assays for the determination of anti-SYD985 antibody responses in Human K2-EDTA plasma are presented.

The analytes showed to be stable in different phases of the process and storage times. The methods are adequate.

Methods used for the PK analysis of both SYD985.001 and SYD985.002 studies, using non-compartmental analysis are adequate for the purpose of reporting PK parameters and characteristics for Total SYD985, Conjugated SYD985, and free toxin (DUBA, SYD986). Study csr-cer-898761-0 (popPK) using a sequential 2-stage approach using nonlinear mixed-effects modelling software (NONMEM) Version 7.4.3 follows usual adequate methodology.

Methods used for the statistical analysis of both SYD985.001 and SYD985.002 studies are adequate for the purpose of reporting PK parameters statistics. Study csr-cer-898761-0 (popPK) follows usual adequate statistical methodology.

Total SYD985

Method validation 1 (VR-LGC-59694) – study SYD985.001

The validated range is 100 ng/mL to 3000 ng/mL in human K2-EDTA plasma. The acceptance criteria were met for accuracy and precision. Inter-assay accuracy of measurement of SYD985 in human K2-EDTA plasma was ±≤10.0 %RE across the five concentrations tested and inter-run CV was ≤11.5%.

The method is not selective for SYD985. It was concluded that trastuzumab (Herceptin), SYD977 and T-DM1 all interfere with the SYD985 total antibody assay, as they all target the same antibody. However, the conjugated SYD985 assay is only selective for SYD985 (the capturing antibody is directed to the linker-drug) and allows discrimination between SYD985 and the other trastuzumab based ADCs. No impact on analysis is expected as treatment with trastuzumab based antibodies or ADCs were not allowed as concomitant medications during the trial. In addition, the interference of prior trastuzumab treatment on total SYD985 plasma levels was taken into account in the Pop-PK modelling of total SYD985.

No interference from circulating HER2-ECD on the SYD985 response of the SYD985 ToTAL, and conjugated antibody assay is observed. No haemolysis or lipemic effect was observed. No hook effect. Dilution linearity was demonstrated by spiking SYD985 in human K2-EDTA plasma matrices at concentrations of 25000 and 250000 ng/mL. The duplicate well CVs and the mean biases of samples prepared at 25000 and 2500000 ng/mL and diluted with matrix buffer were ≤20.0% and within ± 20.0% of the nominal value.

Bench-top stability of SYD985 in human K2-EDTA plasma was evaluated by leaving three replicates of QC samples (prepared and stored at both -20°C and -80°C) at LQC and HQC at processing temperature (room temperature) for 2 and 24 hours before analysis. The effect of freezing and thawing on the stability of SYD985 in human K2-EDTA plasma was evaluated by subjecting three replicates of QC samples at LQC and HQC up to five freeze/thaw cycles at both ≤-20°C and ≤-80°C. SYD985 is stable in human K2-EDTA plasma for at least 770 days when stored at ≤-20°C or ≤-80°C.

Method validation 2 (VR.ABL.79303) – study SYD985.002

The validated range is 100 ng/mL to 3000 ng/mL in human K2-EDTA plasma. The acceptance criteria were met for intra- and inter-accuracy(%bias) and intra- and inter-precision (%CV). The method is not selective for SYD985 either.

No haemolysis or lipemic effect was observed. No hook effect. Compared to method validation 1, dilutional linearity was demonstrated by spiking SYD985 in three independent sources of Human K2 EDTA-Plasma at a concentration of 270.000 ng/mL (QCVHA). The QCVHA was subsequently diluted to nine dilutions (three dilutions over-curve; six dilutions within-curve) with Human K2 EDTA-Plasma. The mean concentrations were compared to the nominal value. The duplicate well CVs and the mean biases of QCVHA prepared at 270.000 ng/mL and additional diluted 2, 10, 50, 125, 200, 300, 400, 600 and 800-fold with matrix buffer were ≤20.0% and within ± 20.0% of the nominal value.

No interference observed for HER2 ECD effect testing. Parallelism and robustness are sufficiently validated.

Conjugated SYD985

Method validation 1 (VR-LGC-59693) – study SYD985001

The validated range is 7.00 ng/mL to 1000 ng/mL in human K2-EDTA plasma. The analytical range for SYD985 conjugated was adjusted from 7.00 – 1000 ng/mL to 7.00 – 400 ng/mL. The adjusted assay range showed good assay performance and could be used for analysis of study samples.

The acceptance criteria were met for intra- and inter-batch accuracy and precision. The accuracy for the QC samples ranged from -20% to 11.7% RE and the precision of the assay was ≤7.2 %CV for the intra-comparison. For the inter-comparison, accuracy for the QC samples ranged from -7.0 to 6.0% RE. The precision of the assay was ≤ 16.0%CV.

No interference from trastuzumab (Herceptin), SYD977 (two lots), SYD989 and T-DM1 (ADC Trastuzumab Emtansine) (all prepared at 7.00 and 1000 ng/mL) on the SYD985 conjugated antibody assay was observed.

No haemolysis effect was observed. Concerning the lipidaemic effect, an additional experiment was done in study LGC267816QB04 as one of the two hyperlipidaemic individuals did not demonstrate selectivity in validation study LGC267816QB02. The eight lipemic K2-EDTA plasma matrices and control plasma pool were spiked at 21.0 ng/mL SYD985 (bias -14.8 to -4.8%, for the eight lipemic plasma samples and -2.4% for the control plasma pool). Dilution linearity was demonstrated by spiking SYD985 in human K2-EDTA plasma matrices at concentrations of 2000 and 20000 ng/mL. Spiked samples with concentrations above the ULOQ up to 500000 ng/mL demonstrated the lack of a high dose Hook effect at the three concentrations tested (bias 0.8 to 3.3%, CV ≤ 3.3%). Parallelism between the calibration curve of the analytical method and samples from clinical study SYD985.001 was assessed. There was no evidence of non-parallelism (see study LGC267816QB04).

SYD985 is stable in human K2-EDTA plasma kept at processing temperature for at least 24 hours. SYD985 is stable in human K2-EDTA plasma after five freeze/thaw cycles when stored at ≤--20°C or ≤-80°C. SYD985 is stable in human K2-EDTA plasma for at least 788 days when stored at ≤-20°C or ≤-80°C.

Method validation 2 (VR-ABL.79304)- study SYD985002

An assay for detecting SYD985 in human K2-EDTA plasma based on the principle of sandwich ELISA. The micro plate is pre-coated with anti-duocarmycin antibody (anti hapten B-6-2-10). After a blocking step and incubation of the plate with antigen (analyte) in samples, bound SYD985 interacts with biotinylated anti-idiotype trastuzumab Fab directed towards the CDR region of SYD985. Incubation with streptavidin labelled horseradish peroxidase (HRP) catalyses a colour development reaction. The intensity of the colorimetric signal is directly proportional to the amount of SYD985 in the standards or samples.

The validated range is 7.00 ng/mL to 1000 ng/mL in human K2-EDTA plasma.

The precision (CV %) was ≤ 20.0% (25.0% for LLOQ and ULOQ) and the accuracy (bias %) was within ±20.0% (±25.0% for LLOQ and ULOQ) of the nominal value for both the between-run and the within-run accuracy and precision.

No interference was observed from T-DM1 (ADC Trastuzumab Emtansine) and trastuzumab (both prepared in the range of 7.00 to 1000 ng/mL) on SYD985 conjugated antibody assay. No interference on the SYD985 conjugated antibody assay from CP-DC1 (DUBA or SYD986) was observed.

No haemolysis or lipemic effect was observed. Regarding dilution linearity, study samples can be quantified using a maximum additional dilution of 12800-fold. (bias -5.2 to 13.3%). The spiked samples with concentrations above the ULOQ demonstrated the lack of a high dose Hook effect in the three matrices tested (three dilutions > ULOQ). The stability of SYD985 in Human K2-EDTA plasma was evaluated by storage of subjecting three replicates of QC samples at 21.0 and 750 ng/mL at ≤-18°C and ≤-70°C for 36, 101, 197, 386, 567 and 731 days.

Incurred sample reanalysis (ISR):

For the clinical study 001 (report BDR.LGC.82957), incurred sample re-analysis was performed in 230/3606 (6.4%) study samples, and 80.9% (186/230) of the incurred samples met the pre-specified criteria. For the phase III study 002 (report CSR.ABL.89872), incurred sample re-analysis was performed in 269/4207 (6.4%) study samples, and 95.5% (257/269) of the incurred samples met the pre-specified criteria. In accordance with the guideline bioanalytical method validation, the concentration obtained for the initial analysis and the concentration obtained by reanalysis were within 30% of their mean for at least 67% of the repeats.

SYD986

VR.ABL.48191

The results presented in the report VR.ABL.48191 demonstrate that the validated method is suitable for the measurement of SYD986 in human K2-EDTA plasma by LC-MS/MS in the concentration range of 1.00 - 200 pg/mL. The method provides selective, precise, accurate, and reproducible measurements. The SYD986 and SYD993 were found to be stable during sample collection, sample handling, sample processing, and after long-term storage at ≤ -18ºC and ≤ -70ºC. In addition, the method showed reproducible recovery (essentially similar for SYD986 and SYD993) and no carry-over.

Pharmacokinetic analyses

In trials SYD985.001 and SYD985.002, total SYD985 (SYD985 with a DAR ≥0), Conjugated SYD985 (SYD985 with a DAR ≥1), and free toxin (DUBA, SYD986) individual plasma concentration-time data were analysed by non-compartmental analysis to characterise the pharmacokinetics (PK) of Total SYD985, Conjugated SYD985, and free toxin.

In each trial, descriptive statistics were used to summarise PK parameters of Total SYD985, Conjugated SYD985, and SYD986 (free toxin). PK parameters were stratified by dose, cycle, study part, and analyte. Individual and mean plasma concentration data were plotted over time by dose, cycle, study part, and analyte.

In study SYD985.001, the PK parameters included (dose-normalised) Cmax, Tmax, (dose-normalised) AUC0-∞, (dose-normalised) AUClast, AUCtau, clearance (CL), distribution volume (Vz) and t½ for Cycle 1 as well as (dose-normalised) Cmax, Tmax, AUClast, and AUCtau for Cycle 2. All area under the curve (AUC) parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentration (linear-up/log-down). The AUC0-last was calculated as the AUC from the time of dosing to the last measurable concentration (Tlast). The AUCtau was calculated as area under the curve from time of dosing to 504 hours after dosing.

In study SYD985.002, for cycles 1, 2 and 4, the PK parameters Cmax, dose-normalised Cmax, Tmax, Cmin, Tlast, Clast, AUClast, AUCtau, AUCinf, dose-normalised AUCinf, CL, CLss, Vss, Vz, terminal rate constant and T1/2 were defined.

Immunogenicity assays

A tiered approach using a homogenous bridging immunogenicity assay format based on the AlphaLISA® technology and including an acid dissociation step has been applied (screening, confirmatory and titre).

In the screening assay, ADA bound to the SYD985-coated acceptor beads and biotinylated-SYD985, forming complexes which were captured onto streptavidin-coated donor beads. This brought the donor and acceptor beads into close proximity. Excitation of the donor beads at 680 nm provoked the release of singlet oxygen molecules that triggered the acceptor beads to emit light at 615 nm when in close proximity. An excess of SYD985 was added for the confirmatory assay (competition principle). A polyclonal rabbit anti-SYD985 antibody (predominantly against trastuzumab) mixed with an anti-hapten B-10-2-6 mouse monoclonal antibody (against seco-DUBA) to monitor the presence of linker-drug conjugated to SYD985 immobilised on acceptor beads and biotinylated SYD985 was used as positive control. The screening and confirmatory assays were validated twice because the samples from SYD985.001 and SYD985.002 trials were analysed by two different contract research organisations (CRO) and assay conditions were slightly changed. The following parameters were established by each CRO: specificity, screening and confirmatory cut points, sensitivity and low positive control (LPC) concentration, selectivity, precision, drug tolerance, end-point titre, stability, prozone/Hook effect and target interference (for SYD985.001, VR.LGC.59695; and for SYD985.002 trial, VR.ABL.79305 and CSR.ABL.89873 (In-study validation)). It was shown that the assays developed for study SYD985.001 can detect antibodies to either linker drug moieties or (mono specifically) to the monoclonal antibody. The method developed for study SYD985.002 was shown to detect antibodies to either linker moiety, drug moiety or (mono-specifically) to the monoclonal antibody. Information on how the mRD has been established has been adequately provided. As requested by CHMP, the applicant has discussed how the interference caused by trastuzumab and T-DM1 is addressed in both clinical studies SYD985.001 and SYD985.002. It can be concluded that previous trastuzumab-related treatment has no impact on the immunogenicity data in study SYD985.002. The potential interference of other concomitant medications is unlikely due to the selectivity of the assay.

Assays to determine the neutralizing capacity of ADAs (cell-based assay format) and for epitope mapping utilizing the earlier described AlphaLISA platform were also developed. Validation of these assays was planned to be executed in case a relevant number of patients would show confirmed positive ADA formation. Validation reports of both the epitope mapping assay (ASR.NL03.90469) and neutralizing antibody assay (ASR.NL03.90470) were finalised. Bioanalytical reports for study sample assay analysis were also finalised. In addition, the overall ADA report (CR.NL03.89705) for Study SYD985.002 was updated, also including remaining ADA sample analysis for patients who remained in the study after submission of the MAA. The updated ADA report also includes an updated integrated analysis of the clinical significance of ADA's raised against SYD985.

As regards the target interference, HER2-ECD concentrations tested up to 93.3 ng/mL do not interfere in the detection of the positive control antibodies at level of HPC 10,000 ng/mL and iLPC 150 ng/mL (both screening and confirmatory assay). In clinical study SYD985.001, HER2 ECD levels were assessed at the start of each cycle. For patients for whom the plasma sHER2 ECD levels were at least once above 93 ng/mL the highest tested sHER2 ECD (n=31 ADA negative patients), the applicant has evaluated the influence of sHER2 ECD and has concluded that these patients did not have any clinical signs that prompted further investigation. The applicant has reported that for the majority of these patients, the concentrations were only slightly > 93 ng/mL. However, it was also found during the validation study that the high concentration of 93 ng/mL HER2-ECD spiked in the negative control screened and confirmed positive (false-positive result). The lower concentration of HER2-ECD tested (9.98 ng/mL) did not screen or confirm positive. Based on the current analysis, no sample confirmed positive in the SYD985.001 trial and thus this is not considered as an issue.

In study SYD985.002, because the number of false-positive patient samples was < 0.5% during the study sample analysis, the screening cut point determined during the validation using plasma from healthy volunteers was found not suitable. To assure that the number of false-positives in an acceptable range, the cut point was re-determined by the applicant using baseline samples from patients from the

SYD985.002 trial. As a consequence, the fixed confirmation cut point also had to be recalculated using the cut point run data from the in-study samples. Furthermore, as the number of freeze and thaw (F/T) cycles exceeded the valid number of six freeze and thaw cycles for a number of study samples, the stability of the positive control antibody for an additional F/T cycles was assessed and found valid.

Drug tolerance was determined up to 10 µg/mL of drug in the screening assay. All PCs with a concentration of 1000 or 3333 ng/mL were positive. But 5 out of 6 samples and 3 out of 6 samples with 100 ng/mL PC were positive in the screening assay a drug concentration of 1.0 µg/mL and 2.0 µg/mL, respectively. All samples with 100 ng/mL PC were positive at 0.2 µg/mL drug. A drug tolerance ranging from 0.2 – 2.0 µg/mL was thus concluded by the applicant. Based on these results, the applicant has flagged the study samples showing a concentration ≥ 2.0 µg/mL of total SYD985. For a total of 4 subjects, all the samples were flagged. The following results at patient level were presented:

Table 4: Subjects classification results summary, excluding flagged results (ADA set)

(excluding ADA sample results when SYD985 Total ≥ 2ug/mL or NR, this results in an ADA set with 274 evaluable subjects)

Classification		n	%
Subject status	ADA negative	257	93.8
	Unevaluable	10	3.6
	ADA inconclusive	5	1.8
	ADA positive	2	0.7
ADA detected	No	263	96.0
	Yes	9	3.3
	NA	2	0.7
Pre-treatment ADA	No	164	59.9
	NA	108	39.4
	Yes	2	0.7
Treatment boosted or induced	NA	272	99.3
	Treatment induced	2	0.7
Transient or persistent response	NA	273	99.6
	Transient response	1	0.4

Listing source: 1.5.2

The target interference was investigated using 10 samples from study SYD985.001 (HER2ECD levels ranging from 19.4 up to 278 ng/mL). The samples with valid results (i.e. with acceptable duplicate CV%) were all screened and confirmed positive for both 150 ng/mL PC and 5000 ng/mL PC levels. Nine of 10 samples non-spiked were negative. Based on these results together with the observation that only 2.1% of HER2 positive metastatic breast cancer patients have levels that exceed 278 ng/mL in trial SYD985.001, the applicant has decided that HER2 ECD would be not measured in study SYD985.002. This approach is deemed reasonable.

Absorption

Absorption, Bioavailability and Bioequivalence as well as Influence of food

SYD985 is intended for IV administration, and therefore, SYD985 is completely bioavailable. Trials to characterise absorption via extravascular routes have not been conducted. This is acceptable.

Table 5: PK parameters built on the basis of study SYD985 (Part I and Part II) results presented in the clinical overview and in the popPK study

		CL (L/h)	V (L)	$t_{1/2}$ (h)	AUC (xg* h/mL)[4]	C_{max} (xg/mL[4]
Total SYD985	Part I	0.044-0.060	3.9-5.4	59-62		
	Part II	0.032-0.052	3.3-4.5	56-79		20-23
	Clinical OV	0.0385[2]	3.47	62.4[2]; 80.3[3];		
	PopPK	0.0385	3.51	(63.2)[1]	2065[5] (1035-3255)	22.8[5] (15.5-32.7)
SYD986	Part I			87-121	2230-2540[5] (1433-4228)	12.4-18.1[5] (7.5-23.5
	Part II			143		16*
	Clinical OV	5.15		144[2]; 123[3]		
	PopPK	172	412	(1.66)[1]	2500	12.9 (7.5-23.5)

(1) estimated from CL and V; (2) based on PopPK; (3) based on Part I; (4) x = µg for SYD985 and x = pg for SYD986; (5) typical values plus p5 and p95

As mentioned by the applicant, there have been no dedicated clinical biopharmaceutic studies (i.e., bioavailability and food effect) for SYD985 to support the MA because the product is administered intravenously (bioavailability=1.0) and no food effect would be expected with parenteral administration.

To demonstrate comparability between drug product used in phase I (frozen solution) and phase III (lyophilised powder) clinical development, analytical comparability studies were performed. Additional analyses of the drug formulation effect on PK were performed following the CHMP request. The analyses are performed in a similar way as the analyses in the POP PK analyses report. Boxplots and a simulation table of total SYD985 steady state exposures indicate that exposures were slightly higher for the lyophilised powder, compared to the frozen solution, but exposure ranges, both of AUC and Cmax were largely overlapping and comparable for both formulations.

In vitro studies indicate that DUBA is unstable in plasma and mainly degraded by non-enzymatic instability. The mechanism by which DUBA is non-enzymatically degraded is by hydrolysis of the amide bond that links the DNA-binding unit to the DNA-alkylating unit. This hydrolysis already takes place at neutral pH and is therefore also expected to take place in vivo in human plasma, which is an aqueous environment with a neutral pH (pH = 7.4).

Distribution

The distribution of both total SYD985 and SYD986 seems well characterised.

Volume of distribution

SYD985

The relatively small volume of distribution is typical of monoclonal antibodies, which are largely confined to the vascular and interstitial spaces due to their large molecular size and poor lipophilicity.

In part I of study SYD985.001, the distribution volume for total SYD985 and conjugated SYD985 ranges between 3.9 L to 5.4 L and 3.2 L to 4.6 L, respectively. In part II, the distribution volume for total

SYD985 and conjugated SYD985 across the cohorts ranged between 3.3 L and 4.5 L and between 3.0 L and 4.6 L, respectively.

In trial SYD985.002, the geometric mean Vz was 0.044 L/kg and 0.046 L/kg for total SYD985 and conjugated SYD985, respectively, following a single dose of SYD985.

No radiolabelled tissue distribution studies for SYD985 have been performed in humans.

The PK profiles of SYD985 are typical for a target mediated drug disposition common to monoclonal antibodies (mAbs).

SYD986

The applicant clarifies that the value of 412 L for the volume of distribution was determined from the IV PK rat study scaled allometrically to a human of 70 kg and that this volume is fixed since it cannot be determined from the model, because the amount of SYD986 released is unknown.

Since the applicant is not aware of any TMDD effect for this free amount, as there is no preclinical data suggesting any nonlinearity in PK after dosing SYD986 and/or SYD978, the high value for Vc/F can be explained on the basis of the target for SYD986 being DNA, which indeed could act as a large sink. On the other hand, the hydrophobic nature of SYD986 can contribute to the high observed value for Vc/F

The two possible explanations for the high value of Vc/F are plausible but the use of rat data to estimate human Vc/F is questionable. However, without any other way to estimate this value, it can be accepted.

Protein binding

Because SYP985 is an antibody, protein binding studies were not conducted which is accepted. SYD986 has high non-specific binding in protein free medium and poor stability in plasma.

Blood to plasma ratio

Blood cell/plasma partitioning studies with [3H]-SYD986 showed a blood/plasma ratio of 0.85, and therefore, it is considered appropriate to analyse plasma as opposed to whole blood for the determination of SYD986 concentrations.

Transporters

SYD986 seems not to be a substrate for the uptake transporters. The effect of efflux transporters was tested. Based on in vitro data, SYD986 is not a substrate for the uptake transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, OATP1B1, and OATP1B3.

See also DDI section.

Elimination

Elimination, excretion and metabolism

The elimination of both total SYD985 and SYD986 seems well characterised.

The fate of SYD985 in humans has not been studied because conventional metabolism and elimination studies are not required for the antibody portion of SYD985 (SYD977).

The assertion that PK of total SYD985 and conjugated are essentially similar can be endorsed.

SYD986 is to be considered a NCE, thus data on its metabolism and excretion in human should be part of the dossier. The applicant was requested to provide a strong justification for the absence of human excretion data and to discuss how findings from animal studies which suggest that majority of SYD985 and SYD986 is excreted in faeces (60-70%) could be extrapolated to humans.

The applicant stated that the lower limits of quantification (LLOQ) achieved in sensitive state of the art LC-MS/MS methods are insufficient to detect the anticipated metabolites in human plasma and excreta. In addition, performing ADME studies using radiolabelled material, as it is the usual case in human studies, is not feasible in end-stage cancer patients. The arguments to support a waiver for human ADME studies were agreed by CHMP in the Scientific Advice EMA/CHMP/SAWP/544332/2019.

The geometric mean plasma terminal half-life of SYD986 was 123.1 h directly from clinical trials and 144 h from popPK estimation. These values are essentially consistent.

The conclusions that (1) SYD986 PK was best described by a 1-compartment model with a Total SYD985 concentration-dependent release rate and first-order elimination and (2) the occurrence of a so-called flip-flop PK behaviour due to simultaneous production of SYD986 (release of SYD986 from SYD985) and elimination can be endorsed.

Metabolism

Preclinical ADME data demonstrate multiple routes of metabolism and excretion of SYD985 and SYD986 exist. The routes and patterns of metabolism were not specially investigated in humans.

Based on these preclinical metabolism data the main in vivo metabolites of SYD985 anticipated in human were described. There are no indications for any human-specific or quantitatively-dominant metabolites in human.

SYD985

SYD985 is composed of the antibody trastuzumab (SYD977), which is covalently bound to a linker drug (SYD980). SYD977 is a protein with an expected metabolic pathway, which results in degradation to peptides and individual amino acids by ubiquitous proteolytic enzymes. Conventional metabolism and elimination studies are not required for the antibody portion of SYD985.

SYD986

An in vitro CYP phenotyping study showed limited contribution of CYP to the overall metabolism of SYD986. None of the other tested CYP enzymes were involved in the metabolism of SYD986. The metabolism of SYD986 by CYP results in 2 metabolites, which were identified and characterised.

Excretion

Total SYD985 and conjugated SYD985

In both Part I and Part II of study SYD985.001, total SYD985 and conjugated SYD985 PK after infusion were characterised by maximum concentrations attained after end of infusion or within a few hours thereafter, and followed by a monophasic log-linear elimination. In part II, the elimination half-life across the cohorts ranged between 56 hours and 79 hours and between 45 hours and 53 hours for total SYD985 and conjugated SYD985, respectively.

In trial SYD985.002, elimination parameters were not adequately characterised for Cycles 2 and 4 due to a limited number of timepoints during this phase. On Cycle 1, the geometric mean plasma half-life was 80.3 hours, 58.1 hours, and 123.1 hours for total SYD985, conjugated SYD985, and SYD986 free toxin, respectively. The geometric mean clearance was 0.0003797 L/h/kg and 0.0005427 L/h/kg for total SYD985 and conjugated SYD985, respectively, on Cycle 1.

Based on the population PK analysis, total SYD985 had a systemic CL of 0.0385 L/hr and an elimination half-life of 2.6 days.

In non-clinical studies, [3H]-SYD985 was excreted to faeces (60%) and urine (26%).

SYD986

SYD986 (free toxin) PK after infusion was characterised by a delay in maximum concentration, which was generally reached within a day after end of infusion, and followed a monophasic log-linear elimination. Elimination half-life roughly ranges between 87 hours to 121 hours. The apparent high elimination half-life was likely the result of both ongoing SYD986 release from available SYD985 and the actual elimination of SYD986. This so-called flipflop PK behaviour occurs when both production of SYD986 (release of SYD986 from SYD985) and elimination occurs at the same time.

In plasma SYD986 is eliminated by hydrolysis and hydrolysis products are excreted to urine. The main metabolites in faeces and bile are described. It is unclear if the metabolite observed in faeces is directly originating from SYD985 or if it is the chlorinated product of SYD986. Since SYD978 is directly converted to SYD986 in buffer at a neutral pH (7.4), it cannot be tested whether SYD978 is a substrate for certain transporters as well.

Based on the population PK analysis, the apparent clearance (CL/F) of the free toxin SYD986 was 5.15 L/hr.

Non-clinical data show that SYD986 is mainly excreted to faeces ([3H]-SYD986 mainly excreted to faeces (77%) and some to urine (6%)) while no mass balance study has been performed in humans due to feasibility issues. Investigation on healthy subjects is not feasible due to obvious safety concerns.

According to the guideline on DDI, contribution of pathways to active metabolites elimination should be estimated. However, besides SYD986, no other active metabolite was identified. With regard to cytotoxic potential, all showed at least a 2000-fold lower in vitro potency in SK-BR-3 cells compared to SYD986 and SYD978.

Consequences of possible genetic polymorphism

SYD986 showed neither inhibition nor time-dependent inhibition towards any CYP enzyme including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5, at concentrations up to 1 µM (490 ng/mL, approximately 30000-fold mean Cmax of SYD986 at 1.2 mg/kg SYD985 in human). Therefore, no effect of genetic polymorphism on metabolism can be envisaged.

Dose proportionality and time dependencies

Dose-proportionality

The pharmacokinetics of total SYD985 assessed by Pop-PK analysis were shown to be dose proportional in the dose range between 1.2 mg/kg and 2.4 mg/kg. PK data from dose levels ≤ 0.6 mg/kg were excluded from the analysis, because only a few subjects were treated with the lowest doses (0.3 and 0.6 mg/kg). As a result, the PK model does not account for any nonlinear PK for doses below 1.2 mg/kg and could not be used to predict dose levels below 1.2 mg/kg.

To evaluate dose proportionality, the AUCtau for cycle 1 based on non-compartmental analysis (NCA) from trial SYD985.001 was used, which included PK data from 3 subjects treated with 0.6 mg/kg. In the SYD985.002 trial there were zero patients treated with 0.6 mg/kg from the start of treatment. Boxplots and summary statistics for the dose normalised AUCtau were created and presented. Dn-AUCtau values for the 3 subjects treated with 0.6 mg/kg were somewhat lower compared to the subjects treated with 1.2 mg/kg but appeared to be in the same range as the dn-AUCtau values observed for 1.5 mg/kg and

1.8 mg/kg. Based on this limited assessment, it is concluded that effects from TMDD, if any, do not result in a clear deviation from dose proportionality for doses of 0.6 mg/kg. An assessment for 0.3 mg/kg was not included since dose reductions to only 0.3 mg/kg are not allowed in the proposed labelling.

Dose levels >1.2 mg/kg of SYD986 do not result in substantial increases in exposure.

PK profiles across cycles are overlapping, indicating time-independent PK for SYD986.

Time dependency

In study SYD985.001, total SYD985, conjugated SYD985, and SYD986 PK were time independent with limited to no accumulation at the tested dose regimen. It was concluded that on average SYD986 exposure did not increase in subsequent dose cycles (SYD986 PK was time-independent).

In study SYD985.002, for total SYD985 and conjugated SYD985, trough concentrations at 3 weeks after dosing appeared to be consistent across consecutive cycles, indicating that there was no substantial accumulation. SYD986 peak concentrations were in the pg/mL range, and exposure was approximately 7000-fold lower compared with conjugated SYD985 exposure based on molar ratio of Cmax. The geometric mean plasma half-life was 123.1 hours for the free toxin SYD986. The maximum concentration was attained at 24 hours post-dose. Average trough concentrations at 3 weeks after dosing were, on average, below the lower limit of quantification and appeared to be consistent across consecutive cycles, indicating that there was also hardly any accumulation of the circulating toxin.

Based on the data collected in studies SYD985.001 and 002 and the POP PK model, there is no substantial accumulation neither for total SYD985 and conjugated SYD985 nor for SYD986.

Pharmacokinetics of metabolites

SYD986 is considered as a metabolite. Due to methodological limitations, besides SYD986, no other main metabolite can be quantified in human plasma, urine, or faeces. In SK-BR-3 cells, besides SYD986, no other active metabolite was identified. With regard to cytotoxic potential, all showed at least a 2000-fold lower in vitro potency compared to SYD986 and SYD978.

Intra and inter-individual variability

Information on intra- and inter-subject variability (based on POP PK analysis) has been adequately added in section 5.2. of the SmPC.

Pharmacokinetics in target population

All PK data have been collected in the target population. The results of the POP PK analysis should be briefly summarised in this section "target population".

●Study csr-cer-898761-0 (popPK)

The steps taken for model building and evaluation are overall supported. A sequential 2-stage approach was applied. First, the total SYD985 PK model was established, fitting the total SYD985 PK data to the model. Subsequently, the model was extended with components for SYD986 PK; individual total SYD985 PK parameter estimates, including the fixed- and random-effects terms, were fixed, and upon addition of SYD986 data, the SYD986 PK parameters were estimated.

Model covariates were selected using univariate screening ($P > 0.05$), followed by stepwise covariate model building (single addition, forward inclusion, and backward elimination), at statistical significance levels of $P < 0.01$ and $P < 0.001$.

Model quality was assessed by inspection of model parameters and their confidence intervals, residual-based goodness-of-fit plots, distributions of random effects, visual predictive checks, and bootstrap analysis.

These steps are considered overall state of the art.

Handling of BLQ is overall acceptable. Concentrations of total SYD985 BLQ during active treatment were excluded during model development, corresponding to the M1 method defined by Beal [6]. The impact of BLQ samples was evaluated for the final model in a sensitivity analysis, applying the M4 method (maximizing the likelihood for all the data treating BLQ observations as censored).

Because the SYD986 model structure was more complex and BLQ samples were expected to have a larger impact on model estimation, BLQ samples were included from the start during model development and applying the M4 method.

However, characterisation of outliers and data exclusion is considered somewhat arbitrary. According to the applicant, total SYD985 data points in the dataset that appear to be outside the norm for that dataset were identified applying following criteria:

• Trough concentrations upon 1.2 mg/kg were generally close to the LLOQ or BLQ. PK samples with a total SYD985 concentration of >15,000 ng/mL at >18 days after dose were defined as an unrealistic high trough concentration.

• Peak concentrations upon 1.2 mg/kg were generally between 20,000 and 30,000 ng/mL. PK samples with a total SYD985 concentration of <1000 ng/mL within 48 hours after dose were defined as an unrealistic low peak concentration.

It was assumed that the recorded sampling time was inconsistent with the dosing time for these samples and occurred as a result of mistakes during sampling time registration and therefore were excluded from the analysis. For consistency, associated SYD986 PK samples with the same sampling date and time were also excluded from the analysis.

All the described assumptions are considered arbitrary and unverified. In particular, the fact that SYD986 PK samples with the same sampling date and time as suspected SYD985 were also excluded from the analysis is considered very bad practice. Likewise, the fact that the impact of these exclusions was not evaluated in the final model is not endorsed.

This said, given the amount of these data, they might not be impacting the final results.

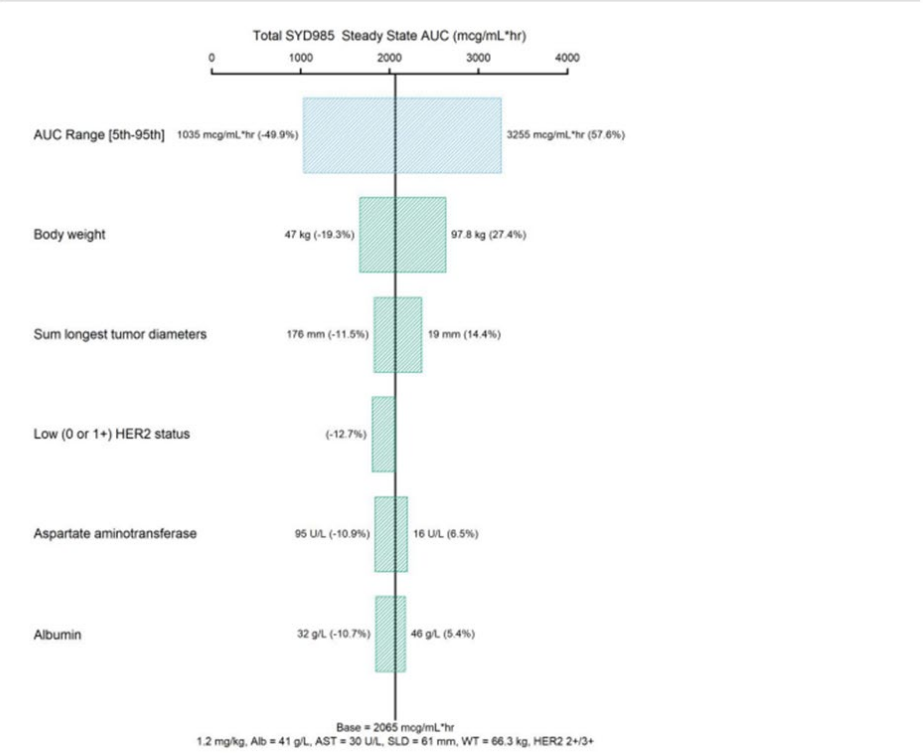
Special populations

Clinical trials were not specifically performed to assess the effects of intrinsic factors on Total SYD985, Conjugated SYD985, or SYD986 PK.

Population PK modelling was used to assess the impact of intrinsic factors on Total SYD985 and SYD986 exposure. Though some covariates in the final SYD985 and SYD986 population PK models showed a difference in exposure, the magnitude of changes in exposure was not considered clinically meaningful as the range of effects was within the observed variability in the modelling dataset for Total SYD985 and SYD986.

Impact of covariates on total SYD985 and SYD986 exposures

Figure 3: Tornado Plot of the Effect of Statistically Significant Covariates on Total SYD985 Steady-State AUC



The dose of SYD985 is based on body weight. Dose adjustments based on other intrinsic factors (age, race, disease characteristics, renal impairment, and hepatic impairment) were not recommended based on model-based analysis of Total SYD985 and SYD986.

Impaired renal and hepatic function

Renal impairment

Given that SYD985 is an IgG1 molecule conjugated to the linker drug SYD980 with a high molecular weight (between 150.7 kDa and 153.7 kDa, depending on glycosylation and DAR), molecules >69 kDa being essentially excluded from glomerular filtration, the lack of dedicated studies in subjects with renal impairment is sufficiently justified. It is not expected to undergo significant renal elimination and its pharmacokinetics is therefore not expected to be impacted by renal impairment.

No subjects with severe renal impairment were included in the studies. The applicant amended the SmPC in sections 4.2, 4.4 and 5.2 accordingly saying that there are no data in patients with severe renal impairment. Trastuzumab duocarmazine should be administered with caution in patients with severe renal impairment.

The effect of renal impairment (subpopulations: normal, mild, and moderate) on Total SYD985 and SYD986 exposure was explored by means of POP PK analysis using subpopulation analyses to predict steady-state post hoc determined AUC and Cmax. Model estimated post hoc SYD985 exposure distributions were overlapping and similar for normal and mild renal impairment subgroups but were somewhat higher for patients with moderate renal impairment for Total SYD985. Post hoc SYD986 exposures were similar across renal impairment subgroups. No dose adjustment is recommended for mild or moderate renal impairment.

Table 6: Model-Predicted Total SYD985 and SYD986 Steady-State Exposure Statistics by Renal Impairment Subpopulation

	Subpopulation	N (%)	AUC (Total SYD985: hr*µg/mL, SYD986: hr*pg/mL)	C_{max} (Total SYD985: µg/mL, SYD986: pg/mL)
Total SYD985	Normal	242 (52.5)	2033 (1067, 3111)	22.8 (15.3, 32.4)
	Mild	189 (41.0)	2055 (1007, 3380)	23.2 (15.4, 33.5)
	Moderate	28 (6.1)	2512 (1756, 3363)	24.8 (21.0, 28.9)
SYD986	Normal	242 (52.5)	2365 (1485, 4226)	12.5 (8.2, 24.5)
	Mild	189 (41.0)	2355 (1420, 3892)	12.6 (7.2, 23.2)
	Moderate	28 (6.1)	2328 (1743, 4464)	11.8 (8.4, 28.5)

Source: CSR.CER.89876, Table 28 and Table 29
Abbreviations: AUC=area under the plasma concentration-time curve; C_{max}=maximum observed plasma concentration; eGFR=estimated glomerular filtration rate; N=number of patients; p5=5th percentile; p95=95th percentile; SYD985=trastuzumab duocarmazine
Notes: Exposure values represent the median (p5, p95). Renal function was missing for 2 patients. Renal impairment classification: Normal = eGFR ≥90 mL/min/1.73 m^2; Mild = eGFR 60 to <90 mL/min/1.73 m^2; and Moderate = eGFR 30 to <60 mL/min/1.73 m^2. There were no patients with eGFR <30 mL/min/1.73 m^2.

Baseline calculated estimated glomerular filtration rate (eGFR) was not found to be a significant factor accounting for between-subject variability in SYD985 or SYD986 PK. The range of eGFR values in trials SYD985.001 and SYD985.002 was 41.1 mL/min/1.73 m2 to 214 mL/min/1.73 m2.

Hepatic impairment

No specific studies have been conducted in study participants to determine the effect of hepatic impairment on the PK of trastuzumab. As a monoclonal antibody, trastuzumab is not expected to undergo significant hepatic elimination and the lack of dedicated studies in subjects with hepatic impairment is justified.

Baseline AST was a predictor for Total SYD985 and SYD986 PK, and baseline bilirubin was a predictor for SYD986 PK. The majority of the analysis dataset consisted of patients with normal hepatic function and mild hepatic impairment according to the National Cancer Institute Organ Dysfunction Working Group classification. There were 2 patients with moderate hepatic impairment. No patients with severe hepatic impairment were enrolled. Post hoc model estimates shows the Total SYD985 and SYD986 steady-state exposures analysed by hepatic function impairment subgroups. Total SYD985 exposure distributions were largely overlapping and comparable for patients with normal, mild, and moderate hepatic function.

Mean SYD986 exposures were somewhat higher in patients with mild hepatic impairment compared to patients with normal hepatic function, with a substantial overlap in the range, indicating that mild hepatic impairment has no marked effect on the exposure of SYD986. No dose adjustment is therefore recommended for mild hepatic impairment.

Data from subjects with moderate hepatic impairment are very sparce (n=2). SYD986 exposure was substantially higher for the 2 patients with moderate hepatic impairment. Therefore, no definitive conclusions regarding the effect of moderate hepatic impairment on the exposure of SYD986 can be drawn and no dose adjustment can be recommended given the small number of patients/limited data available (see SmPC).

Table 7: Model-Predicted Total SYD985 and SYD986 Steady-State Exposure Statistics SYD986 by Hepatic Impairment Subpopulation

	Subpopulation	N (%)	AUC (Total SYD985 hr*µg/mL SYD986 hr*pg/mL)	C_{max} (Total SYD985 µg/mL, SYD986 pg/mL)
Total SYD985	Normal	325 (70.5)	2141 (1197, 3356)	23.5 (16.6, 32.8)
	Mild	133 (28.9)	1860 (831, 3043)	22.5 (14.5, 31.8)
	Moderate	2 (0.4)	1788 (1544, 2032)	22.2 (21.1, 23.2)
SYD986	Normal	325 (70.5)	2249 (1408, 3777)	11.7 (7.3, 19.9)
	Mild	133 (28.9)	2662 (1694, 4874)	15.4 (9.3, 29.7)
	Moderate	2 (0.4)	6504 (5343, 7664)	37.8 (28.5, 47.0)

Source: CSR.CER.89876, Table 30 and Table 31
Abbreviations: AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; C_{max}=maximum observed plasma concentration; N=number of patients; NCI-ODWG=National Cancer Institute Organ Dysfunction Working Group; p5=5th percentile; p95=95th percentile; ULN=upper limit of normal
Notes: Exposure values represent the median (p5, p95). Hepatic function was missing for 1 patient. Hepatic impairment classification based on NCI-ODWG criteria: Normal = (bilirubin and AST ≤ULN) and Mild = ([bilirubin >ULN to 1.5 × ULN] or [bilirubin ≤ULN and AST >ULN]). There were no patients with severe hepatic impairment. AST ULN = 41 U/L and bilirubin ULN = 1.23 mg/dL.

Gender, Race, Weight, Age

Analyses of the gender effect on PK were performed, in a similar way to the analyses in the POP PK analyses report. The simulation tables (Table 22 and Table 23) and boxplots (data not shown) of total SYD985 and SYD986 steady state exposures indicate that exposures were overlapping and comparable for Female and Male subjects for total SYD985 and SYD986.

Table 8: Exposure statistics Total SYD985 by Sex

Subpopulation	N (%)	AUC µg·h/mL	Cmax µg/mL
Female	429 (93.1%)	2094 (1055, 3287)	23.3 (15.3, 32.7)
Male	32 (6.9%)	1682 (977, 2512)	21.2 (17.8, 27.7)

Simulation run: PopPK-985-986-simulations-final-run31-run220-EMArequest-dec2022.rmd
Notes: Each exposure is modeled for a 1.2 mg/kg Q3W dosing regimen using each subject's estimated PK parameters. Exposure values represent the median (p5, p95).
Abbreviations: AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; N=number of subjects; p5=5th percentile; p95=95th percentile; SYD985=[vic-]trastuzumab duocarmazine

Table 9: Exposure statistics SYD986 by sex

Subpopulation	N (%)	AUC pg·h/mL	Cmax pg/mL
Female	429 (93.1%)	2367 (1435, 4180)	12.5 (7.5, 23.4)
Male	32 (6.9%)	2159 (1504, 4519)	12.6 (8.6, 32.2)

Simulation run: PopPK-985-986-simulations-final-run31-run220-EMArequest-dec2022.rmd
Notes: Each exposure is modeled for a 1.2 mg/kg Q3W dosing regimen using each subject's estimated PK parameters. Exposure values represent the median (p5, p95).
Abbreviations: AUC=area under the plasma concentration-time curve; Cmax=maximum concentration; N=number of subjects; p5=5th percentile; p95=95th percentile; SYD986=free toxin duocarmazine

Nine male subjects were enrolled in part I and 26 male subjects were enrolled in part II of study 001. Information on the comparable exposure for Male and Female subjects should be provided in the SmPC.

The two studies included a large majority of white patients. Race effect on PK was reported in the popPK analysis.

Race was not found to be a significant covariate in total SYD985 or SYD986 PK. Model-predicted steady-state post hoc total SYD985 and SYD986 exposure measures grouped by race (White, Non-White, and Non-disclosed) showed no trends. No dose adjustment is recommended.

Increasing body weight leads to slightly increasing exposure of total trastuzumab duocarmazine but had no impact on DUBA exposure.

SYD985 is dosed based on body weight. Baseline weight was a significant covariate, accounting for between-subject variability for drug CL and total volume of SYD985 and release rate of SYD986 in population PK modelling. Both Total SYD985 and SYD986 steady-state AUC and maximum concentration were found to increase with increased body weight, with largely overlapping ranges of exposure. At the 5th and 95th percentiles of the observed weight distribution in trials SYD985.001 and SYD985.002 (47 kg to 97.8 kg), Total SYD985 and SYD986 steady-state exposure and maximum concentration were within the ranges of the typical population.

Table 10: Model-Predicted Total SYD985 and SYD986 Steady-State Exposure Statistics by Body Weight Subpopulation

	Subpopulation (kg)	N (%)	AUC (hr*µg/mL)	C_{max} (µg/mL)
Total SYD985	<50	41 (8.9)	1473 (650, 2579)	18.2 (13.4, 24.1)
	50-65	168 (36.4)	1904 (1077, 3069)	21.1 (15.6, 27.1)
	65-80	161 (34.9)	2149 (1238, 3332)	24.7 (18.6, 33.0)
	>80	91 (19.7)	2504 (1497, 3432)	27.7 (20.1, 35.8)
SYD986	<50	41 (8.9)	2207 (1304, 3465)	11.0 (7.1, 23.5)
	50-65	168 (36.4)	2280 (1434, 3937)	11.8 (7.4, 26.4)
	65-80	161 (34.9)	2408 (1499, 3701)	12.7 (8.0, 22.8)
	>80	91 (19.7)	2552 (1724, 4767)	13.5 (8.6, 23.5)

Source: CSR.CER.89876, Table 22 and Table 23
Abbreviations: AUC=area under the plasma concentration-time curve; C_{max}=maximum observed plasma concentration; N=number of patients; p5=5th percentile; p95=95th percentile
Notes: Exposure values represent the median (p5, p95).

Although the variability in AUC and Cmax is larger using NCA (see Table 24), this variability is less than a two-fold difference and could be expected based on the used methodologies. Using PopPK simulations, the variability in AUC and Cmax is comparable to the variability of CL and Vss (Table 25).

Table 1: PK parameters for total SYD985 using NCA

NCA estimate	SYD985.001 (N=151)	SYD985-002 (N=285)	Overall (N=436)
Cmax (ng/mL)			
Mean (SD)	22.9 (6.84)	29.0 (10.6)	26.8 (9.83)
Median (CV%)	21.9 (29.8)	26.8 (36.4)	24.9 (36.7)
[Min, Max]	[11.6, 45.8]	[8.08, 92.5]	[8.08, 92.5]
Missing	1 (0.7%)	21 (7.4%)	22 (5.0%)
AUCtau (mcg/mL.hr)			
Mean (SD)	2190 (1110)	3580 (2640)	2980 (2220)
Median (CV%)	1980 (50.5)	2720 (73.9)	2390 (74.7)
[Min, Max]	[738, 6770]	[728, 15900]	[728, 15900]
Missing	30 (19.9%)	126 (44.2%)	156 (35.8%)
CL (L/hr)			
Mean (SD)	0.0425 (0.0161)	0.0285 (0.0124)	0.0338 (0.0154)
Median (CV%)	0.0425 (38.0)	0.0292 (43.4)	0.0347 (45.7)
[Min, Max]	[0.00928, 0.116]	[0.00226, 0.0733]	[0.00226, 0.116]
Missing	55 (36.4%)	126 (44.2%)	181 (41.5%)
Vss (L)			
Mean (SD)	3.95 (0.989)	3.01 (1.09)	3.36 (1.14)
Median (CV%)	3.91 (25.0)	2.92 (36.1)	3.31 (34.0)
[Min, Max]	[1.60, 7.62]	[1.01, 10.7]	[1.01, 10.7]
Missing	55 (36.4%)	126 (44.2%)	181 (41.5%)

Based on subjects treated with 1.2 mg/kg

Table 2: PK parameters for total SYD985 using PopPK simulations

PopPK estimate	SYD985.001 (N=178)	SYD985.002 (N=283)	Overall (N=461)
Cmax (ng/mL)			
Mean (SD)	22.9 (5.62)	24.2 (5.46)	23.7 (5.55)
Median (CV%)	22.3 (24.6)	23.7 (22.6)	23.0 (23.4)
[Min, Max]	[12.1, 53.7]	[12.5, 50.7]	[12.1, 53.7]
AUCtau (mcg/mL.hr)			
Mean (SD)	1880 (624)	2270 (732)	2120 (717)
Median (CV%)	1810 (33.2)	2200 (32.2)	2070 (33.9)
[Min, Max]	[524, 3650]	[642, 6640]	[524, 6640]
CL (L/hr)			
Mean (SD)	0.0507 (0.0183)	0.0372 (0.0108)	0.0424 (0.0156)
Median (CV%)	0.0475 (36.1)	0.0364 (29.1)	0.0390 (36.8)
[Min, Max]	[0.0209, 0.148]	[0.0131, 0.0823]	[0.0131, 0.148]
Vss (L)			
Mean (SD)	3.90 (0.797)	3.35 (0.582)	3.56 (0.724)
Median (CV%)	3.81 (20.4)	3.34 (17.4)	3.49 (20.3)
[Min, Max]	[1.58, 6.74]	[1.52, 5.60]	[1.52, 6.74]

Based on simulations of 1.2 mg/kg for all subjects for which posthocs were available

The variability of the different PK parameters seems to be within acceptable limits both in the NCA and pop-PK calculations.

Elderly

Age was not found to be a significant covariate in Total SYD985 or SYD986 PK in patients ranging in age from 23 years to 80 years. Model-predicted steady-state post hoc Total SYD985 and SYD986 exposure measures grouped by age showed no trends. Dose adjustment is not recommended.

As requested, the table below has been completed with the information from the SYD985.001 and SYD985.002 trials. The two below-mentioned trials were the two trials for which PK data has been provided in the dossier.

Table 3: Age distribution in the PK trials (PK set)

PK Trials	Age 65-74 (older subjects number/ Total number)	Age 75-84 (Older subjects number/ Total number)	Age 85+ (Older subjects number/ Total number
SYD985.002 (SYD985 arm)	50/283	16/283	0/283
SYD985.001*	39/185	6/185	0/185

* One patient (3012041, 74 year old) is included in the PK set but not in the NCA analyses as reported in CSR.SHH.83978 since actual dose deviated >20% from planned dose.

Children

The safety and efficacy in children and adolescents below 18 years of age have not been established. No data are available.

Disease characteristics

Due to the predicted minimal impact of SLD and HER2 status on Total SYD985 and SYD986 exposure, no dose adjustment is recommended based on PK differences driven by disease characteristics.

Pharmacokinetic interaction studies

In vitro and animal data support the conclusions on drug-drug interactions, namely that, at clinically relevant concentrations, inhibition of transporters and CYP enzymes (and induction as well) is unlikely to occur in clinical use. Therefore, SYD986 is unlikely to be a perpetrator or victim of CYP-mediated drug-drug interaction. During the two clinical studies SYD985.001 and SYD985.002, no restrictions were made on comedications related to potential interactions since the risk of any interaction potential was regarded to be very low.

Prior treatment with pertuzumab within 1 year before the start of SYD985 treatment showed no trends in predicted steady-state post hoc Total SYD985 and SYD986 exposure measures. Grouping of patients by the last prior treatment being trastuzumab, trastuzumab emtansine, or trastuzumab deruxtecan was also not associated with any trends in predicted steady-state post hoc Total SYD985 and SYD986 exposure measures.

<u>In vitro</u>

<u>SYD985</u>

Not applicable.

<u>SYD986</u>

Given the relatively high potency and low systemic exposure of cytotoxic payloads, drug–drug interaction (DDI) considerations for ADCs are rather different from traditional small molecule therapeutics.

Intestinal DDIs could be excluded since SYD985 is administered IV.

<u>-SYD986 as perpetrator</u>

With regards to the potential risk of SYD986 being a perpetrator drug the risk is considered very low. In vitro, SYD986 did not show any CYP induction (no mRNA induction in cryopreserved human

hepatocytes at 0.2 – 50 nM SYD986) or CYP inhibition (in pooled human liver microsomes at 0.1 – 1000 nM) and is therefore unlikely to be a perpetrator of CYP-mediated drug-drug interaction.

SYD986 as a CYP inducer:

The effects of SYD986 on the activities of CYP1A2, CYP2B6, and CYP3A4/5 was evaluated in cryopreserved human hepatocytes from 3 male donors. Because significant cytotoxic effects on the human hepatocytes were observed at concentrations of 100 and 1000 nM SYD986, it was decided to perform the assessment of SYD986-mediated CYP induction with concentrations of SYD986 of 0.2, 0.5, 2, 5, 10, 20 and 50 nM (24 ng/ml, 1250-fold mean Cmax at 1.2mg/kg)). No precipitation or insoluble material was observed in any of the solutions tested.

In line with EMA guidance, the in vitro study is considered positive for enzyme induction if the test compound gives rise to a more than 100% increase in mRNA and the increase is concentration dependent.

No increases in CYP1A2 mRNA levels were observed following treatment of hepatocytes from donors 1 and 2 with 0.2 to 50 nM SYD986. An increase in CYP1A2 mRNA levels was observed following treatment of hepatocytes from donor 3 with 20 nM SYD986 (2.35-fold). However, the increase was seen only with this concentration of SYD986, was not dose-related and therefore can be considered a negative finding. The values for omeprazole-mediated CYP1A2 induction (AhR-mediated) ranged from 30.5 to 163- fold increase with 50 µM omeprazole.

No increases in CYP2B6 mRNA levels were observed following treatment of hepatocytes from donor 2 with 0.2 to 50 nM SYD986. An increase in CYP2B6 mRNA level was observed following treatment of hepatocytes from donors 1 and 3. Maximum increases of 19.7-fold in donor 1 (with 50 nM SYD986) and of 39.9-fold in donor 3 (with 20 nM SYD986) were seen. However, these increases were not dose-related and therefore can be considered a negative finding. The values for phenobarbital-mediated CYP2B6 induction (CAR-mediated) ranged from 8.34 to 148-fold increase with 1 mM phenobarbital.

No increases in CYP3A4 mRNA levels were observed following treatment of hepatocytes from donor 2 with 0.2 to 50 nM SYD986. An increase in CYP3A4 mRNA level was observed following treatment of hepatocytes from donors 1 and 3. Maximum increases of 4.05-fold in donor 1 (with 5 nM SYD986) and of 14.2-fold in donor 3 (with 20 nM SYD986) were seen. However, these increases were not dose-related and therefore can be considered a negative finding. The values for rifampicin-mediated CYP3A4 induction (PXR-mediated) ranged from 12.5 to 18.8- fold increase with 25 µM rifampicin.

These data demonstrate that SYD986 is not an inducer of CYP1A2, CYP2B6, or CYP3A4CYP3A4/5 at concentrations like 0.2 (0.098 ng/mL), 0.5, 2,5,10,20 and 50 nM (24 ng/mL) in human hepatocytes. The concentrations studied are higher than the Cmax of SYD986 at 1.2 mg/kg in man. The concentrations of 0.2 to 50 µM correspond to approximately 5 to 1250-fold the clinical Cmax of SYD986 at 1.2 mg/kg SYD985 (12-18 pg/mL). The culture time of 72 hours is standard. Because the highest plasma value found in clinical studies was approx. 18 pg/mL, an interaction due to enzyme induction is unlikely at this very low concentration.

The positive controls (inducers) chosen (rifampicin, phenobarbital and omeprazole) are deemed acceptable. Flumazenil is accepted as negative inducer control.

To determine whether SYD986 had any cytotoxic properties towards human hepatocytes, cell viability was assessed after the 72 hour exposure, using the cell proliferation assay AQueous One Solution (Promega). The viability of the hepatocytes following exposure to SYD986 at the top two concentrations used (20 and 50 nM) was assessed on Day 1 and 72 hours after dosing on Day 1 in donors 1, 2 and 3. The conclusions drawn from donor 1 and 2 are valid at Day 4. The conclusions

drawn from donor 3 concerning CYP induction are assumed to be valid for SYD986 at concentrations lower than 20 nM.

SYD986 as a CYP inhibitor:

The effect of SYD986 at concentrations of up to 1000 nM on the activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 in pooled human liver microsomes was investigated in study. To this end, SYD986 (0, 0.1, 1, 10, 100, 300 and 1000 nM) was incubated with pooled human liver microsomes, β-NADPH, phosphate buffer and adequate CYP-selective chemical substrates. The concentration range tested in this study included much higher concentrations of SYD986 than the clinical concentrations.

To confirm the suitability, adequate positive controls were used. No time-dependent inhibition has been detected.

SYD986 did not inhibit CYP enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, at concentrations up to 1 µM (490 ng/mL, approximately 25000-fold mean Cmax of SYD986 at 1.2 mg/kg SYD985 in man).

CYP enzyme	Selective substrate	Reaction	Selective inhibitor	
			Direct	Time-dependent
CYP1A2	Phenacetin (20 µM)	O-Deethylation to acetaminophen	α-Naphthoflavone	Furafylline
CYP2B6	Bupropion (80 µM)	Hydroxylation to hydroxybupropion	NA	Phencyclidine
CYP2C8	Amodiaquine (2 µM)	N-deethylation to N-desethylamodiaquine	Quercetin	Phenelzine
CYP2C9	Tolbutamide (200 µM)	Hydroxylation to 4′-hydroxytolbutamide	Sulphaphenazole	Tienilic acid
CYP2C19	S-Mephenytoin (20 µM)	Hydroxylation to 4′-hydroxy-S-mephenytoin	Modafinil	Ticlopidine
CYP2D6	Bufuralol (10 µM)	Hydroxylation to 1′-hydroxybufuralol	Quinidine	Paroxetine
CYP3A4/5*	Testosterone (75 µM)	Hydroxylation to 6β-hydroxytestosterone	Ketoconazole	Azamulin
	Midazolam (5 µM)	Hydroxylation to 1′-hydroxymidazolam		

* multiple substrates to assess CYP3A4/5 interactions
NA – no direct inhibitor of CYP2B6 available

SYD986 as a transporter inhibitor:

SYD986 was not a (relevant) inhibitor of the tested transporters OAT1, MATE1, MATE2-K, BSEP, BCRP, P-gp, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 at 10 uM. Furthermore, plasma levels of SYD986 are extremely low (geomean Cmax 16.8 pg/mL, CV = 61%), and the multiple metabolic routes for SYD986 (nonenzymatic and enzymatic hydrolysis in plasma, glutathione conjugation and sulfation) are very unlikely to be saturated by these low levels.

-SYD986 as victim

CYP isoenzymes and GST:

SYD986 is unlikely to be a victim of CYP-mediated drug-drug interaction. An in vitro CYP phenotyping study showed limited contribution of CYP to the overall metabolism of SYD986. None of the other tested CYP enzymes were involved in the metabolism of SYD986.

The metabolism of SYD986 by CYP resulted in 2 metabolites which were identified. The two metabolites observed after incubation of 0.1 µM SYD986 with recombinant CYP, were not observed after incubation in (human) hepatocytes in vitro (at 0.1 and 1 µM). In human hepatocytes, the major metabolic pathways were identified. Except for one, these metabolic routes were also observed in vivo in CES1c KO mice. The CYP metabolites were not observed. This suggests the relevance of this CYP450 pathway in SYD986 clearance in vivo is limited.

An in vitro phenotyping study using recombinant GSTs was performed.

However, SYD986 levels after dosing SYD985 are too low to cause and/or detect any formation of the Phase-II metabolites.

Efflux transporters:

SYD986 efflux was studied in cell-monolayer assays at relatively high concentrations ranging from 1 to 10 µM, in the presence of 4% bovine serum albumin (BSA). SYD986 was determined to be a substrate for certain transporters.

The relevant concentrations for evaluation of a drug as a transporter substrate in vitro are normally the clinical relevant concentrations. The concentrations used in the experiments are sufficiently justified and it is sufficiently proved that the monolayer integrity is kept in the presence of 1µM SYD986.

Uptake transporters:

Based on in vitro data, SYD986 is not a substrate for the uptake transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, OATP1B1, and OATP1B3.

In vivo

The risk of clinically significant drug-drug interactions is judged low by the applicant and specific clinical trials on potential drug-drug interactions were not performed.

Exposure relevant for safety evaluation

Significant Exposure Response relationships were observed for ocular toxicity (SOC level) and keratitis (PT level) with Total SYD985 exposure, with increasing probability (or hazard) of an event associated with increasing exposure. E-R analysis showed that ocular toxicity and keratitis are not related to SYD986 exposure.

Total SYD985 exposure was not a significant predictor of ILD/pneumonitis any grade or LVEF decrease to <50% events.

3.3.1.2. Pharmacodynamics

Mechanism of action

SYD985 is an antibody-drug conjugate (ADC) that belongs to the class of HER2 inhibitors.

SYD985 is an ADC comprising the humanised immunoglobulin G1 (IgG1) monoclonal antibody (mAb) trastuzumab (SYD977) covalently bound to a linker-drug SYD980. The ADC targets the human epidermal growth factor receptor 2 (HER2) via trastuzumab (similar to Herceptin) and delivers the toxic drug payload DUocarmycin-hydroxyBenzamide-Azaindole (DUBA) (SYD986), a DNA alkylating agent that damages DNA in both dividing and nondividing cells, leading to cell death.

After binding to HER2 on the cell membrane, SYD985 undergoes receptor-mediated internalisation and the linker is cleaved at the dipeptide valine-citrulline motif in the lysosome by proteases, such as cathepsin B. Subsequently, two self-elimination reactions occur to generate the prodrug (seco-DUBA, SYD978), which then spontaneously rearranges to form the active toxin (DUBA, SYD986). Alternatively, after linker cleavage, self-elimination and rearrangement may occur in a concerted process, in which SYD986 is directly formed. The active toxin (DUBA, SYD986) binds in the minor groove of DNA and

alkylates adenine-N3 resulting in DNA damage and ultimately cell death in both dividing and non-dividing cells.

Primary and Secondary pharmacology

Efficacy

A summary of the results from the primary efficacy E-R analysis based on the ICR assessed endpoints is shown in the table below. Generally, a trend toward increased efficacy with increased Total SYD985 exposure was observed, reaching statistical significance for PFS and clinical response. Based on SYD986 exposure, the E-R relationships were mostly flat, with a statistically significant decrease in duration of response with increased exposure.

Table 4: Summary of the Primary Efficacy E-R Analysis

Efficacy Endpoint	Parameter	$TAE_{985,Cycle1}$	$TAE_{986,Cycle1}$
PFS	Direction of trend hazard	down	up
	P value	0.00141	0.0949
Clinical response	Direction of trend odds ratio	up	down
	P value	0.0388	0.617
Clinical benefit	Direction of trend odds ratio	up	down
	P value	0.121	0.224
Duration of response	Direction of trend slope	down	down
	P value	0.149	0.042

Source: CSR.CER.89877, Table 19
Abbreviations: E-R=exposure-response; PFS=progression-free survival; TAE_{985}=time-averaged exposure of Total SYD985; TAE_{986}=time-averaged exposure of SYD986
Notes: Up = upward trend, increasing hazard, odds ratio, or slope with increasing exposure; down = downward trend, decreasing hazard, odds ratio, or slope with increasing exposure.

Model-based predictions based on the primary analysis for efficacy endpoints at the 10th, 50th, and 90th percentiles of the total SYD985 exposure range following 1.2 mg/kg SYD985 Q3W are presented in Table below. The effect of total SYD985 was most pronounced for PFS. At the lower 10th percentile PFS was 4.2 months compared to 6.9 months at the 50th percentile. For clinical response, clinical benefit, and duration of response, effects were less pronounced, and the confidence intervals (CIs) at the 10th and 50th percentiles were largely overlapping, indicating that the clinical relevance of these effects may be limited within the observed exposure range upon 1.2 mg/kg Q3W.

Table 5: Model-Predicted Response (95% CI) for Efficacy Endpoints for Total SYD985

Efficacy Endpoint	10th Percentile of Exposure Range (95% CI)	50th Percentile of Exposure Range (95% CI)	90th Percentile of Exposure Range (95% CI)
PFS (months)	4.20 (3.31, 5.84)	6.92 (6.59, 6.95)	9.70 (7.25, 11.8)
Clinical response (proportion)	0.188 (0.128, 0.258)	0.235 (0.188, 0.288)	0.307 (0.239, 0.381)
Clinical benefit (proportion)	0.341 (0.262, 0.448)	0.386 (0.331, 0.448)	0.443 (0.366, 0.532)
Duration of clinical response (months)	4.97 (3.46, 6.28)	4.34 (3.45, 5.23)	3.58 (2.56, 4.57)

Source: Sections 5.1.3, 5.1.4, 5.1.5, and 5.1.6
Abbreviations: CI=confidence interval; PFS=progression-free survival; SYD985=[vic-]trastuzumab duocarmazine

Safety

A summary of the results from the primary safety E-R analysis is shown in table below. Significant E-R relations were observed for eye toxicity and keratitis-related safety endpoints with total SYD985 exposure, with increasing probability (or hazard) of an event associated with increasing exposure. These assessments were generally similar between the primary and secondary analyses.

Table 6: Summary of the primary Safety E-R Analysis

Safety Endpoint	Parameter	$TAE_{985,Cycle1}$	$TAE_{986,Cycle1}$
ILD/pneumonitis all grades	Direction of trend odds ratio	Up	Down
	P-value	0.0681	0.640
Eye toxicity Grade ≥3	Direction of trend odds ratio	Up	Down
	P-value	0.00595	0.173
Eye toxicity Grade ≥3, excluding keratitis	Direction of trend odds ratio	Up	Down
	P-value	0.0258	0.269
Keratitis Grade ≥2	Direction of trend odds ratio	Up	Down
	P-value	0.00269	0.0644
Time to keratitis Grade ≥2	Direction of trend hazard	Up	Down
	P-value	0.00340	0.953
LVEF decrease to <50%	Direction of trend odds ratio	Down	Down
	P-value	0.606	0.0133
Dose modification	Direction of trend hazard	Up	Up
	P-value	0.314	0.126

Source: Sections 5.2.2.1, 5.2.2.2, 5.2.2.3, 5.2.2.4, 5.2.2.5, 5.2.2.6, and 5.2.3
Notes: Upward trend = increasing odds ratio or hazard with increasing exposure; downward trend = decreasing odds ratio or hazard with increasing exposure.
Abbreviations: E-R=exposure-response; ILD=interstitial lung disease; LVEF=left ventricular ejection fraction; SYD985=[vic-]trastuzumab duocarmazine; SYD986=free toxin duocarmazine; $TAE_{985,Cycle1}$=time-averaged exposure during Cycle 1 for total SYD985; $TAE_{986,Cycle1}$=time-averaged exposure during Cycle 1 for SYD986

In the primary analysis for ILD/pneumonitis all grades, no exposure effect was found. However, the secondary analyses, pooling data from Studies SYD985.001 and SYD985.002, indicated that total SYD985 exposure is a predictor of ILD/pneumonitis all grades, with increasing probability of an event with increasing exposure. Total SYD985 was not a predictor of LVEF decrease to <50%. However, the trend should be interpreted with care given the low number of events.

Based on SYD986 exposure, the E-R relationships were flat for ILD/pneumonitis all grades, eye toxicity Grade ≥3, eye toxicity Grade ≥3, excluding keratitis, keratitis Grade ≥2 (both incidence and onset time), and time to first dose modification. For LVEF decrease to <50%, a significant downward trend with SYD986 exposure was observed, with a decreasing probability of event with increasing exposure. However, the trend should be interpreted with care given the low number of events.

No covariates were identified as predictors for any of the endpoints for which a statistically significant E-R relationship was observed.

Model-based predictions based on the primary analysis for safety endpoints at the 10th, 50th, and 90th percentiles of the total SYD985 exposure range following 1.2 mg/kg SYD985 Q3W are presented in table below.

Table 7: Model-Predicted Response (95% CI) for Safety Endpoints Using TAE985, Cycle 1

Safety Endpoint	10th Percentile of Exposure Range (95% CI)	50th Percentile of Exposure Range (95% CI)	90th Percentile of Exposure Range (95% CI)
ILD/pneumonitis all grades events (proportion)	0.0536 (0.0261, 0.0993)	0.0757 (0.0487, 0.117)	0.114 (0.0740, 0.174)
Eye toxicity Grade ≥3 events (proportion)	0.140 (0.0869, 0.206)	0.194 (0.150, 0.249)	0.284 (0.214, 0.363)
Eye toxicity Grade ≥3, excluding keratitis events (proportion)	0.0798 (0.0451, 0.129)	0.112 (0.0790, 0.155)	0.169 (0.119, 0.233)
Keratitis Grade ≥2 events (proportion)	0.160 (0.108, 0.247)	0.225 (0.179, 0.283)	0.328 (0.255, 0.417)
Time to first keratitis Grade ≥2 events (months)	12.23 (11.44, 14.98)	11.31 (11.24, 11.31)	8.959 (7.636, 9.653)
LVEF decrease to <50% events (proportion)	0.0372 (0.0146, 0.106)	0.0318 (0.0172, 0.0628)	0.0264 (0.00831, 0.0759)
Time to first dose modification (months)	5.12 (4.30, 6.98)	4.89 (4.76, 5.02)	4.30 (4.13, 5.12)

Source: Sections 5.2.2.1, 5.2.2.2, 5.2.2.3, 5.2.2.4, 5.2.2.6, and 5.2.3
Abbreviations: CI=confidence interval; ILD=interstitial lung disease; LVEF=left ventricular ejection fraction; SYD985=[vic-]trastuzumab duocarmazine; $TAE_{985,Cycle1}$=time-averaged exposure during Cycle 1 for total SYD985

At the 90th percentile versus the 50th percentile, an absolute increase of 10.3% for keratitis Grade ≥2 incidence was predicted. For eye toxicity Grade ≥3 and eye toxicity Grade ≥3, excluding keratitis, absolute increases of the incidence were 9.0% and 5.7%, respectively. For ILD/pneumonitis all grades and LVEF decrease to <50%, the absolute increases were <5%.

At the higher 90th percentile, time to onset of the first event of keratitis Grade ≥2 was 8.96 months compared to 11.3 months at the 50th percentile.

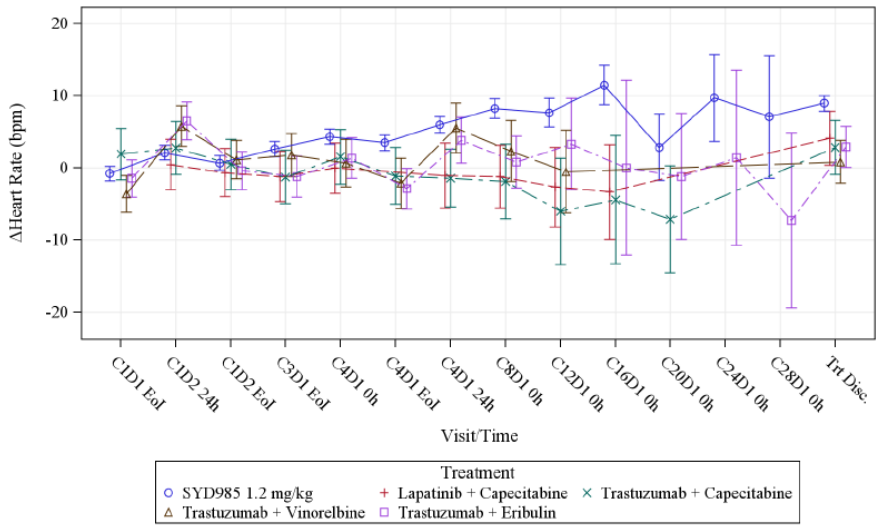
ECG and QTc evaluation

In the SYD985.002 study, central ECG review was included. ECGs were transmitted to a centralised ECG core lab for blinded evaluation including interval duration measurements using a superimposed global median beat measurement methodology and review by a cardiologist. No separate, thorough QT/QTc evaluation trial was performed, but an intensified ECG assessment schedule in cycles 1 and 4 was implemented in the phase III protocol to evaluate the potential effect of SYD985 on QTc interval.

- *Effect on Heart Rate*

There was no evidence of a clinically significant effect of SYD985 on heart rate. The averaged mean rate change from baseline for HR in the SYD985 treatment group was 3.3 bpm, and the largest least squares (LS) mean change from baseline for HR ranged from -0.8 bpm (C1D1 end of infusion, n = 276) to 11.5 bpm (C16D1; n = 21).

Figure 4: Change from Baseline- ΔHeart Rate (bpm) versus timepoints (Estimates are mixed model based) ECG Analysis Population



- *Effect on Cardiac conduction (PR and QRS)*

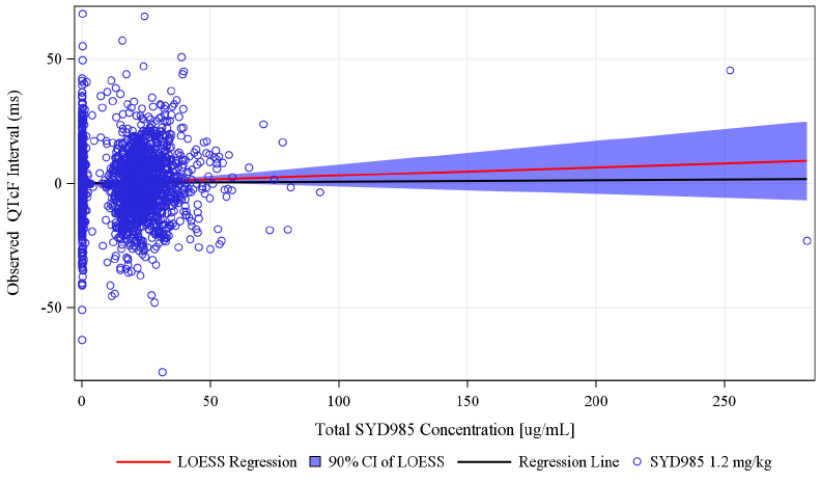
SYD985 treatment had no clinically significant effect on heart rate or cardiac depolarisation (as reflected by the PR interval and QRS duration).

- *Effect on Cardiac repolarisation (QTcF)*

The by time point analysis demonstrated no evidence of clinically meaningful QTc prolongation, with the 90% 2-sided upper confidence interval for QTcF change from baseline < 10 ms at all post dose timepoints.

The concentration-QTc modelling predictions of QTc increases from baseline at the geometric Cmax for SYD986 and total SYD985 were -1.5 ms (90% UCI -0.5 ms) and 0.7 ms (90% UCI 1.6 ms) respectively. The model also predicted that the 90% 2-sided upper confidence bound for ΔQTcF remains < 10 ms at SYD986 concentrations up to approximately 50-60 pg/mL. According to the responses to D120, at a total SYD985 concentration up to 100 µg/mL, the 90% UCI for ΔQTcF was below 10 ms based on the concentration-QTc model, taking into account that the highest Cmax observed was < 80 µg/mL.

Figure 5: Scatter Plot of Observed Total SYD985 Concentration (ug/mL) and QTcF Interval (ms) with SLR and LOESS Regression in Primary SLR Model- PK/PD Population.



An effect of SYD985 on heart rate is shown with a larger mean rate change from baseline compared to the physician's choice treatment groups, i.e. 3.3 bpm in SYD985 group, 1.1 bpm for trastuzumab+eribulin, 0.9 bpm for trastuzumab+vinorelbine, 0.8 bpm for trastuzumab+capecitabine and 0.3 bpm for lapatinib+capecitabine. The tachycardia categorical outlier criteria was met in 21 patients (7.4%) and there was a higher incidence of TEAE tachycardia in the SYD985 group compared to the physician's choice group (7 patients [2.4%] vs 1 patient [0.7%], respectively).

Table 8: Time-averaged mean change from baseline, categorical outlier, and ECG morphologic analyses

	SYD985 1.2 mg/kg	Lapatinib+ Capecitabine	Trastuzumab+ Capecitabine	Trastuzumab + Vinorelbine	Trastuzumab + Eribulin
Total N	287	26	23	42	43
Heart Rate in bpm (mean change from baseline)	3.3	0.3	0.8	0.9	1.1
Heart Rate tachycardic outliers, N	3 (1.0%)	0	0	0	0
Heart Rate bradycardic outliers, N (%)	21 (7.3%)	1 (3.8%)	0	1 (2.4%)	2 (4.7%)
PR interval in ms (mean change from baseline)	-1.8	-2.3	5.0	2.5	3.8
PR interval outliers, N (%)	1 (0.3%)	0	1 (4.3%)	0	1 (2.3%)
QRS duration in ms (mean change from baseline)	-1.1	-0.5	1.0	1.9	1.1
QRS duration outliers, N (%)	1 (0.3%)	0	0	0	0
QTcF interval in ms (mean change from baseline)	-0.3	-1.0	-4.7	-4.5	0.6
QTcF new >500 ms, N (%)	0	0	0	0	0
QTcF new >480 ms, N (%)	2 (0.7%)	0	0	0	1 (2.3%)
QTcF >30-≤60 ms N (%)	30 (10.5%)	1 (3.8%)	0	1 (2.4%)	5 (11.6%)
QTcF >60 ms, N (%)	2 (0.7%)	0	0	0	0
New Atrial Fibrillation, N (%)	0	0	0	0	0
New Atrial Flutter, N (%)	0	0	0	0	0
New abnormal U waves, N (%)	0	0	0	0	0
New ST segment depression changes, N (%)	22 (7.8%)	0	1 (4.3%)	2 (4.9%)	3 (7.0%)
New ST segment elevation changes, N (%)	0	0	0	0	0
New T wave inverted or report of ischemia, N (%)	7 (2.5%)	0	1 (4.3%)	1 (2.4%)	2 (4.7%)
New 2nd Degree Heart Block, N	0	0	0	0	0
New 3rd Degree Heart Block, N	0	0	0	0	0
New complete RBBB, N (%)	1 (0.4%)	0	1 (4.3%)	0	0
New complete LBBB, N (%)	0	0	0	0	0
New MI, N (%)	3 (1.1%)	0	0	0	0

Source: Appendix Tables 14.1.1 – 14.3.9, RBBB= Right Bundle Branch Block, LBBB= Left Bundle Branch Block

3.3.2. Discussion on clinical pharmacology

Methods

The validations of the bioanalytical methods for (1) Total trastuzumab Fab antibody LTMB ELISA for the determination of total SYD985 concentrations; (2) conjugated antibody assay (coated anti-duocarmycin LTMB ELISA) method for the determination of conjugated SYD985 concentrations; (3) LC-MS/MS method for the determination of free SYD986 concentrations; and (4) AlphaLisa Immunogenicity assays for the determination of anti-SYD985 antibody responses in Human K2-EDTA plasma were presented. The analytes showed to be stable in different phases of the process and storage times. The methods are adequate.

Methods used for the PK analysis of both SYD985.001 and SYD985.002 studies, using non-compartmental analysis are adequate for the purpose of reporting PK parameters and characteristics for Total SYD985, Conjugated SYD985, and free toxin (DUBA, SYD986). Study csr-cer-898761-0 (popPK) using a sequential 2-stage approach using nonlinear mixed-effects modelling software (NONMEM) Version 7.4.3 follows usual adequate methodology.

Methods used for the statistical analysis of both SYD985.001 and SYD985.002 studies are adequate for the purpose of reporting PK parameters statistics. Study csr-cer-898761-0 (popPK) follows usual adequate statistical methodology.

Regarding the immunogenicity assays, a number of issues were identified mainly related to the potential interference of drug on board in study samples as well as previous and concomitant medications. The applicant has adequately discussed how the interference caused by trastuzumab and T-DM1 is addressed in both clinical studies SYD985.001 and SYD985.002. It can be concluded that previous trastuzumab-related treatment has no impact on the immunogenicity data in study SYD985.002. The potential interference of other concomitant medications is unlikely due to the selectivity of the assay.

Moreover, the confirmatory cut point using a 1% false-positive rate (instead of the tighter 0.1% false-positive rate) was requested to be recalculated and an updated integrated analysis of the clinical significance of immunogenicity results was requested to be provided for the study SYD985.001. An overview of the screening and confirmatory baseline study sample results was adequately provided. In the confirmatory assay, all screening-positive samples were found negative.

Absorption, Bioavailability and Bioequivalence as well as Influence of food

SYD985 is intended for IV administration, and therefore, SYD985 is completely bioavailable. Trials to characterise absorption via extravascular routes have not been conducted. This is acceptable.

Distribution

The distribution of both total SYD985 and SYD986 seems well characterised.

For **total SYD985**: The assertion that PK of total SYD985 and conjugated are comparable can be endorsed. Volume of distribution value appears to be consistent across the different studies, supporting the typical value from popPK, showing that total SYD985 has a limited volume of distribution of 3.51 L, typical of large protein drugs, which distribute primarily to the blood and interstitial spaces.

A blood/plasma ratio of 0.85 for **SYD986** supports the assertion that it was considered appropriate to analyse plasma as opposed to whole blood for the determination of SYD986 concentrations.

For SYD986, the high value of 412 L may be indicative of target-mediated drug disposition (TMDD). The applicant clarified that the value of 412 L for the volume of distribution was determined from the IV PK rat study scaled allometrically to a human of 70 kg and that this volume was fixed since it could not be determined from the model, because the amount of SYD986 released is unknown. As there was no preclinical data suggesting any nonlinearity in PK after dosing SYD986 and/or SYD978, the high value for Vc/F was explained on the basis of the target for SYD986 being DNA, which indeed could act as a large sink. On the other hand, the hydrophobic nature of SYD986 can contribute to the high observed value for Vc/F. The two possible explanations for the high value of Vc/F are plausible but the use of rat data to estimate human Vc/F is questionable.

Elimination, excretion and metabolism

The elimination of both total SYD985 and SYD986 seems well characterised.

The assertion that PK of total SYD985 and conjugated are essentially similar can be endorsed. Clearance values appear to be consistent across the different studies, supporting the typical value from popPK: 0.0385 L/h. However, the value estimated from popPK (62.4 h) appears to be representative of the half-life for SYD985.

The geometric mean plasma terminal half-life of **SYD986** was 123.1 h directly from clinical trials and 144 h from popPK estimation. These values are essentially consistent.

The conclusions that (1) SYD986 PK was best described by a 1-compartment model with a Total SYD985 concentration-dependent release rate and first-order elimination and (2) the occurrence of a so-called flip-flop PK behaviour due to simultaneous production of SYD986 (release of SYD986 from SYD985) and elimination can be endorsed. A very short half-life value (1.66 h) as estimated from popPK values for volume and clearance, seems to support the hypothesis of a flip-flop PK behaviour.

It is acceptable that no urinary or faecal recovery study of **SYD985** has been performed.

As for **SYD986** the in vitro and non-clinical as well as limited Phase III metabolism data seem to support the contents of the renal impairment section.

The fate of SYD985 in humans has not been studied because, as the applicant states, conventional metabolism and elimination studies are not required for the antibody portion of SYD985 (SYD977) and have not been performed.

SYD986 metabolism has been studied in vitro and in a mouse study. Limited data from the phase III trial confirms low clinical risk for drug-drug interaction. Although a mass balance study has been performed in rat, the metabolic and elimination pathway in man might be different. The applicant was asked to discuss how findings from animal studies which suggest that majority of SYD985 and SYD986 is excreted in faeces (60-70%) could be extrapolated to humans. The applicant provided an extensive body of evidence and argumentation supporting a waiver for human ADME, which is considered acceptable and in line with the Scientific Advice (EMA/CHMP/SAWP/544332/2019).

Consequences of possible genetic polymorphism

SYD986 showed neither inhibition nor time-dependent inhibition towards any CYP enzyme including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5, at concentrations up to 1 µM (490 ng/mL, approximately 30000-fold mean Cmax of SYD986 at 1.2 mg/kg SYD985 in human). Therefore, no effect of genetic polymorphism on metabolism can be envisaged.

Dose proportionality and time dependency

The applicant provides data supporting dose proportional PK in the dose range from 1.2 mg/kg to 2.4 mg/kg for total **SYD985.** However, at lower dose levels (0.3 mg/kg, 0.6 mg/kg) nonlinear PK were observed. PK data from dose levels ≤ 0.6 mg/kg were excluded from the analysis, because only a few subjects were treated with the lowest doses (0.3 and 0.6 mg/kg). Boxplots and summary statistics for the dose normalised AUCtau were created and presented, based on non-compartmental analysis (NCA) from trial SYD985.001, which included PK data from 3 subjects treated with 0.6 mg/kg. Based on this limited assessment, it is concluded that effects from TMDD, if any, do not result in a clear deviation from dose proportionality for doses of 0.6 mg/kg. The applicant provided limited evidence to support that there is no clear deviation from dose proportionality for doses of 0.6 mg/kg. In view of the scarcity of data, this can be accepted. However, it should be clear in the SmPC that doses below 1.2 mg/kg should be used with strict caution.

Consistency of low accumulation of trough concentrations across the consecutive cycles from studies SYD985.001 and SYD985.002 support the total SYD985 and conjugated SYD985 PK time independency. PK profiles across cycles are overlapping, indicating time-independent PK for SYD986.

Impaired renal and hepatic function

No subjects with serious renal impairment were included in the studies. This has been clarified in relevant sections of the SmPC.

The applicant was requested to further elaborate on all existing data to justify that no dose adjustment is necessary in patients with moderate renal impairment. Sufficient sets of data enabling a good perspective on the impact of renal impairment on the most common TEAEs related to treatment and exposure of SYD985 and SYD986 were provided together with a thorough discussion on moderate renal impairment patients, due to the low number of patients included in this category. In view of the small subset of patients studied with moderate renal impairment conclusions on observed differences should be made with appropriate caution and are not considered to require extensive additional guidance in the proposed SmPC can be accepted.

Total SYD985 exposures were similar across the subgroups with different levels of hepatic insufficiency. It appears that the impact of increased AST or decreased albumin on decreased exposure of SYD985 did not reach a significant level on AUC and C_{max}.

In the case of SYD986, there is a low impact of increased bilirubin on exposure and a slight and substantial increase of exposure in mild and moderate hepatic impairment respectively in 2 subjects. The SmPC has been adequately updated in this regard.

Gender, Race, Weight, Age

Since the two clinical studies included a large majority of female patients, gender effect on PK was not reported. Since a further analysis of the gender effect has been performed and the exposures were overlapping and comparable for Female and Male subjects for total SYD985 and SYD986, this finding should be included with appropriate words in the SmPC (OC).

The two studies included a large majority of white patients. Race effect on PK was reported in the popPK analysis. There are no significant differences between the different groups considered.

A modest and low impact of body weight on exposures of total SYD985 and SYD986 respectively was found. However, an increase of ca. 27-28% of Cmax and AUC of SYD985 respectively is considered significant and has been mentioned in the SmPC.

SYD985 is dosed based on body weight.

The variability of the different PK parameters seems to be within acceptable limits both in the NCA and pop-PK calculations. Regarding impact of variability on body weight-based dosing, the applicant showed, by simulations using different dosing strategies based on different ways to calculate body weight, that although capped dosing, and dosing by LBM or IBM did reduce the variability in AUC and Cmax, these alternative dosing regimens did not seem to improve the benefit/ risk ratio.

No significant differences have been found for different age subpopulations.

The E-R popPK analysis was conducted on both SYD985.001 and SYD985.002 studies.

Efficacy

• Total SYD985 exposure was a predictor of PFS and clinical response, with increased exposure resulting in increased efficacy.

• Total SYD985 exposure effects were not statistically significant for clinical benefit and duration of clinical response.

• For SYD986 exposure, the efficacy E-R relationships were generally flat. Exposure effects were not statistically significant for PFS, clinical response, or clinical benefit.

Safety

• Total SYD985 exposure was a predictor of the eye toxicity-related endpoints, including eye toxicity Grade ≥3 and eye toxicity Grade ≥3 but excluding keratitis, and keratitis Grade ≥2,

• Total SYD985 exposure was a significant predictor neither of ILD/pneumonitis any grade and LVEF decrease to <50% events, nor of time to first dose modification.

• The safety E-R relationships were generally flat for SYD986 exposure. Exposure effects were not statistically significant for ILD/pneumonitis any grade, eye toxicity Grade ≥3, and eye toxicity Grade ≥3, excluding keratitis, keratitis Grade ≥2, and time to first dose modification.

• SYD986 exposure effects were statistically significant for LVEF decrease to <50%, with higher exposures resulting in a decreasing incidence of events, but the trend should be interpreted with care given the low number of events.

Central evaluation showed that SYD985 treatment had no clinically significant effect on heart rate or cardiac depolarisation (as reflected by the PR interval and QRS duration). SYD985 treatment demonstrated no evidence of a clinically significant effect on cardiac repolarisation. The by timepoint analysis demonstrated no evidence of clinically meaningful QTc prolongation, with the 90% 2-sided upper confidence interval for QTcF change from baseline < 10 ms at all post dose timepoints. However, in the concentration-QTc modelling the 90% 2-sided upper confidence bound for ΔQTcF exceeded 10 ms at the highest SYD985 concentrations.

The number of cardiac disorders reported in the phase III trial with SYD985 was generally low. In the phase III trial, the numbers for ejection fraction decreased were low and a change in LVEF does not seem to be an important safety concern for SYD985 in patients with a baseline LVEF value of 50% or higher. No clinically significant effects of SYD985 on cardiac depolarisation and repolarisation were observed based on central assessment of collected ECGs in the phase III trial (see clinical safety, Table 766).

Overall, the numbers for ejection fraction decreased were low and a change in LVEF did not seem to be a safety concern for SYD985 in patients with a baseline LVEF value of 50% or higher.

A clinically significant effect of SYD985 on heart rate considering the change on HR from baseline more pronounced in SYD985 group than the comparators, the tachycardia categorical outlier criteria met in 21 patients (7.4%) and the higher incidence of TEAE tachycardia in the SYD985 group compared to the physician's choice group (7 patients [2.4%] vs 1 patient [0.7%], respectively).

3.3.3. Conclusions on clinical pharmacology

General conclusions on Pharmacokinetics

In spite of its complexity (4 analytical methods, 3 analytes to be studied) the PK of SYD985 and related species have been adequately approached by the applicant. No critical findings in the different aspects covered, namely special populations, drug-drug interactions and Dose proportionality and time dependency. Other concerns arising from this assessment should be addressed by the applicant.

General conclusions on Pharmacodynamics

The totality of the results from the E-R analysis suggests that for most of the efficacy and safety endpoints, an upward trend is present for total SYD985 exposure but the E-R relationship is generally flat for SYD986. These data indicate that efficacy and safety effects appear more causally to total SYD985 exposure rather than to the SYD986 exposure. Total SYD985 exposure was a predictor of PFS and clinical response, with increased exposure resulting in increased efficacy. Total SYD985 exposure effects were not statistically significant for clinical benefit and duration of clinical response.

3.3.4. Clinical efficacy

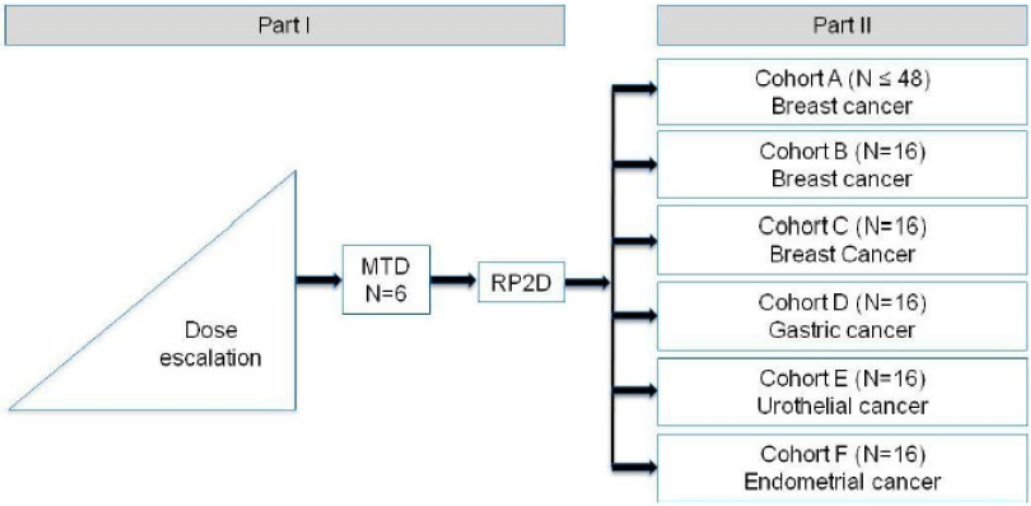
3.3.4.1. Dose-response study (SYD985.001)

Study SYD985.001 was an open-label, single-arm, first-in-human study to evaluate the safety, PK, and preliminary efficacy of SYD985. The study consisted of 2 parts: Part I was the dose-escalation phase, and Part II was the expanded cohort phase (see study design below).

In Part I, patients with locally advanced or metastatic solid tumours of any origin could have been enrolled, whereas in Part II, only patients with locally advanced or metastatic breast (cohort A to C), gastric (cohort D), urothelial (cohort E), or endometrial cancer (cohort F) were eligible. Please note that HER2+ breast cancer patients were only included in the cohort A (where three different dosing regimens were tested in three cohorts A1, A2, A3, see below). Cohort B and C included HER2-low, HR-positive or negative breast cancer patients respectively.

Part I of this study was conducted by 3 Principal Investigators at 3 sites in 3 countries: The Netherlands (1 site), Belgium (1 site), and United Kingdom (1 site). Part II of this study was conducted by 15 Principal Investigators at 15 sites in 4 countries: The Netherlands (4 sites), Belgium (3 sites), United Kingdom (4 sites), and Spain (4 sites).

Figure 6: Study design



MTD = maximum tolerated dose; RP2D = recommended phase II dose

The primary objectives of this study were:

- To evaluate the safety of SYD985 infusions administered every 3 weeks and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). The MTD was defined as the highest dose level at which dose limiting toxicities (DLTs) occurred in not more than 1 out of 6 patients during Cycle 1 (Part I [dose escalation]).
- To evaluate the objective tumour response rate (ORR) (Part II [expanded cohorts]).

The secondary objectives of this study were to evaluate for SYD985:

- Safety (Part II)
- Pharmacokinetic (PK) parameters
- Immunogenicity
- Efficacy
- Quality of life (QoL)

In Part I, at least 3 patients were to be enrolled at each dose level (0.3mg/kg to 2.4mg/kg). The MTD was defined as the highest dose level at which no more than 1 out of 6 patients experienced a DLT. The RP2D was to be determined based on all available safety and PK data. Patients received infusions of SYD985 every 3 weeks until disease progression or unacceptable toxicity (Q3W).

Part II of the study consisted of 6 cohorts based on cancer type and histological characteristics. Patients in Part II received the RP2D. Three different dosing regimens were evaluated in Cohort A. Patients to be enrolled in Part II Cohort A were randomly assigned in a 1:1:1 ratio to 1 of the following subgroups:

- A1 – SYD985 RP2D every 3 weeks (further selected with RP2D)
- A2 – SYD985 RP2D every 3 weeks for 4 cycles, followed by a **reduced** dose every 3 weeks
- A3 – SYD985 RP2D every 3 weeks for 4 cycles, followed by the **same** dose every 6 weeks

Patients in the other cohorts received the SYD985 RP2D every 3 weeks.

Results

A total of 186 patients were enrolled in SYD085.001 (185 dosed) with 40 patients enrolled in Part I (39 dosed) and 146 patients enrolled in Part II (all dosed). Part II patients received SYD985 at the dose of 1.2 mg/kg (selected RP2D), administered by intravenous infusion once every 3 weeks, except for patients in Cohort A2 who received 0.9 mg/kg SYD985 after Cycle 4 and patients in Cohort A3 who received 1.2 mg/kg SYD985 infusions every 6 weeks after Cycle 4. A total of 50 patients were included in the HER2+ breast cancer cohort (A) with 17 patients in the cohort A1, 17 patients in the cohort A2 and 16 patients in the cohort A3.

Efficacy

Objective Response Rate

The ORR is the percentage of patients with measurable disease according to RECIST at Baseline with a best objective response of CR or PR.

Part I (solid tumours of any origin)

A total of 6 patients (17.6%) of the 34 patients in the Full Analysis Population who had measurable disease according to RECIST achieved a confirmed response. All of these responders were patients with breast cancer.

The estimate of the confirmed ORR was 17.6% (95% CI: 6.8; 34.5). The estimate of the confirmed plus unconfirmed ORR was 32.4% (95% CI: 17.4; 50.5). It is agreed that there was no clear increase of ORR with increasing dose. The lowest dose at which a response was observed was 1.2 mg/kg. For the subgroup of 22 patients with breast cancer that was measurable according to RECIST (of which 7 were HER2-negative) the estimate of the confirmed ORR was 27.3% (95% CI: 10.7; 50.2). The estimate of the confirmed plus unconfirmed ORR was 45.5% (95% CI: 24.4; 67.8). The lowest dose at which a response was observed was 1.2 mg/kg. There was no clear relationship between dose and ORR.

Table 9: Primary Efficacy Parameter Secondary Analysis: Objective Response Rate. Part I - Full Analysis Population

	Part I SYD985 Dose Level						
Objective Response Rate	**Total N=34**	**0.3 mg/kg N=3**	**0.6 mg/kg N=3**	**1.2 mg/kg N=6**	**1.5 mg/kg N=9**	**1.8 mg/kg N=10**	**2.4 mg/kg N=3**
Confirmed Responder, n (%)	6 (17.6)	0	0	2 (33.3)	0	4 (40.0)	0
Unconfirmed Responder, n (%)	5 (14.7)	0	0	1 (16.7)	0	2 (20.0)	2 (66.7)
Estimate of Confirmed ORR	17.6%	0.0%	0.0%	33.3%	0.0%	40.0%	0.0%
95% Confidence Limits	6.8 – 34.5	0.0 – 70.8	0.0 – 70.8	4.3 – 77.7	0.0 – 33.6	12.2 – 73.8	0.0 – 70.8
Estimate of Confirmed and Unconfirmed ORR	32.4%	0.0%	0.0%	50.0%	0.0%	60.0%	66.7%
95% Confidence Limits	17.4 – 50.5	0.0 – 70.8	0.0 – 70.8	11.8 – 88.2	0.0 – 33.6	26.2 – 87.8	9.4 – 99.2

n = number of patients in specified category; N = total number of patients; ORR = objective response rate.
Source: Table 14.2.1.3

Table 20: Primary Efficacy Parameter Secondary Analysis: Objective Response Rate. Part I - All Breast Cancer Patients Full Analysis Population

	Part I SYD985 Dose Level						
Objective Response Rate	**Total N=22**	**0.3 mg/kg N=2**	**0.6 mg/kg N=1**	**1.2 mg/kg N=5**	**1.5 mg/kg N=6**	**1.8 mg/kg N=6**	**2.4 mg/kg N=2**
Confirmed Responder, n (%)	6 (27.3)	0	0	2 (40.0)	0	4 (66.7)	0
Unconfirmed Responder, n (%)	4 (18.2)	0	0	1 (20.0)	0	1 (16.7)	2 (100)
Estimate of Confirmed ORR	27.3%	0.0%	0.0%	40.0%	0.0%	66.7%	0.0%
95% Confidence Limits	10.7 – 50.2	0.0 - 84.2	0.0 - 97.5	5.3 - 85.3	0.0 - 45.9	22.3 - 95.7	0.0 - 84.2
Estimate of Confirmed and Unconfirmed ORR	45.5%	0.0%	0.0%	60.0%	0.0%	83.3%	100.0%
95% Confidence Limits	24.4 - 67.8	0.0 - 84.2	0.0 - 97.5	14.7 - 94.7	0.0 - 45.9	35.9 - 99.6	15.8 - 100

n = number of patients in specified category; N = total number of patients; ORR = objective response rate.
Source: Table 14.2.1.4

Part II

A total of 31 patients (22.1%) of the 140 patients in the Full Analysis Population who had measurable disease according to RECIST achieved a confirmed response with 29.2% of the patients in cohort A (A1: 37.5%; A2: 29.4%; A3: 20.0%). An additional 10 patients (7.1%) achieved an unconfirmed response with 2 patients (4.2%) in Cohort A (A1: 0%; A2: 5.9%; A3: 6.7%).

The estimate of the confirmed ORR was 22.1% (95% CI: 15.6; 29.9). The estimate of the confirmed plus unconfirmed ORR was 29.3% (95% CI: 21.9; 37.6). The estimates of the confirmed plus unconfirmed ORR per cohort in the Cohort A was 33.3% showing additional benefit for breast cancer patients. Within Cohort A, the frequency of patients who achieved a confirmed response was somewhat lower in Cohort A2 and A3.

Table 10: Primary Efficacy Parameter Primary Analysis: Objective Response Rate. Part II – Full Analysis Population

	Part II Cohort									
Objective Response Rate	**Total N=140**	**A N=48**	**A1 N=16**	**A2 N=17**	**A3 N=15**	**B N=32**	**C N=15**	**D N=16**	**E N=16**	**F N=13**
Confirmed Responder, n (%)	31 (22.1)	14 (29.2)	6 (37.5)	5 (29.4)	3 (20.0)	5 (15.6)	4 (26.7)	0	3 (18.8)	5 (38.5)
Unconfirmed Responder, n (%)	10 (7.1)	2 (4.2)	0	1 (5.9)	1 (6.7)	4 (12.5)	2 (13.3)	1 (6.3)	1 (6.3)	0
Estimate of Confirmed ORR	22.1%	29.2%	37.5%	29.4%	20.0%	15.6%	26.7%	0.0%	18.8%	38.5%
95% Confidence Limits	15.6 - 29.9	17.0 - 44.1	15.2 - 64.6	10.3 - 56.0	4.3 - 48.1	5.3 - 32.8	7.8 - 55.1	0.0 - 20.6	4.0 - 45.6	13.9 - 68.4
Estimate of Confirmed and Unconfirmed ORR	29.3%	33.3%	37.5%	35.3%	26.7%	28.1%	40.0%	6.3%	25.0%	38.5%
95% Confidence Limits	21.9 - 37.6	20.4 - 48.4	15.2 - 64.6	14.2 - 61.7	7.8 - 55.1	13.7 – 46.7	16.3 - 67.7	0.2 - 30.2	7.3 - 52.4	13.9 - 68.4

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; n = number of patients in specified category; N = total number of patients; ORR = objective response rate.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer; Cohort C = HER2-low, HR-negative breast cancer;
Cohort D = gastric cancer; Cohort E = urothelial cancer; Cohort F = endometrial cancer.
Source: Table 14.2.1.1

Clinical Benefit Rate (CBR)

The CBR was defined as the percentage of patients with CR, PR, SD or non-CR/non-PD (SD or non-CR/non-PD for 6 or more months).

Part I (solid tumours of any origin)

A total of 12 patients (32.4%) of the 37 patients in the Full Analysis Population achieved clinical benefit. The estimate of CBR was 32.4% (95% CI: 18.0; 49.8). The lowest dose at which clinical benefit was observed was 1.2 mg/kg. There was no clear increase of CBR with increasing dose.

For the subgroup of 25 patients with breast cancer in the Full Analysis Population, 10 patients (40.0%) achieved clinical benefit. The estimate of CBR was 40.0% (95% CI: 21.1; 61.3). The lowest dose at which clinical benefit was observed was 1.2 mg/kg. There was no clear relationship between dose and CBR.

Table 11: Secondary Efficacy Parameter 1 Clinical Benefit Rate (CBR). Part I (Full Analysis Population)

		Part I SYD985 Dose Level					
CBR [1]	Part I Total N=37	0.3 mg/kg N=3	0.6 mg/kg N=3	1.2 mg/kg N=6	1.5 mg/kg N=11	1.8 mg/kg N=11	2.4 mg/kg N=3
Clinical Benefit							
Yes	12 (32.4)	0	0	4 (66.7)	0	6 (54.5)	2 (66.7)
No	25 (67.6)	3 (100)	3 (100)	2 (33.3)	11 (100)	5 (45.5)	1 (33.3)
Estimate of CBR	32.4%	0.0%	0.0%	66.7%	0.0%	54.5%	66.7%
95% Confidence Limits [2]	18.0 - 49.8	0.0 - 70.8	0.0 - 70.8	22.3 - 95.7	0.0 - 28.5	23.4 - 83.3	9.4 - 99.2

Table 12: Secondary Efficacy Parameter 1 Clinical Benefit Rate (CBR). Part I - Breast Cancer Patients (Full Analysis Population)

All Breast Cancer Patients

		Part I SYD985 Dose Level					
CBR [1]	Part I Total N=25	0.3 mg/kg N=2	0.6 mg/kg N=1	1.2 mg/kg N=5	1.5 mg/kg N=8	1.8 mg/kg N=7	2.4 mg/kg N=2
Clinical Benefit							
Yes	10 (40.0)	0	0	3 (60.0)	0	5 (71.4)	2 (100)
No	15 (60.0)	2 (100)	1 (100)	2 (40.0)	8 (100)	2 (28.6)	0
Estimate of CBR	40.0%	0.0%	0.0%	60.0%	0.0%	71.4%	100.0%
95% Confidence Limits [2]	21.1 - 61.3	0.0 - 84.2	0.0 - 97.5	14.7 - 94.7	0.0 - 36.9	29.0 - 96.3	15.8 - 100

Part II

Within Cohort A, the frequency of patients who achieved clinical benefit was higher in the Cohort A2 (76.5%) *versus* Cohort A1 (56.3%) and A3 (50%).

Table 13: Secondary Efficacy Parameter 1 Clinical Benefit Rate (CBR). Part II (Full Analysis Population)

		Part II Cohort			
CBR [1]	Part II Total N=141	A N=49	A1 N=16	A2 N=17	A3 N=16
Clinical Benefit					
Yes	60 (42.6)	30 (61.2)	9 (56.3)	13 (76.5)	8 (50.0)
No	81 (57.4)	19 (38.8)	7 (43.8)	4 (23.5)	8 (50.0)
Estimate of CBR	42.6%	61.2%	56.3%	76.5%	50.0%
95% Confidence Limits [2]	34.3 - 51.2	46.2 - 74.8	29.9 - 80.2	50.1 - 93.2	24.7 - 75.3

Best Overall Tumour Response

Part I (solid tumours of any origin)

The lowest dose level at which PR was achieved was 1.2 mg/kg. The lowest dose at which SD was achieved was 0.3 mg/kg. There was no clear relationship between response and dose level.

Table 14: Secondary Efficacy Parameter 2 Best Overall Tumour Response. Part I (Full Analysis Population)

		Part I SYD985 Dose Level					
Best Overall Tumour Response	Part I Total N=37	0.3 mg/kg N=3	0.6 mg/kg N=3	1.2 mg/kg N=6	1.5 mg/kg N=11	1.8 mg/kg N=11	2.4 mg/kg N=3
Confirmed [1]							
Complete Response	0	0	0	0	0	0	0
Partial Response	6 (16.2)	0	0	2 (33.3)	0	4 (36.4)	0
Stable Disease	20 (54.1)	3 (100)	1 (33.3)	4 (66.7)	7 (63.6)	4 (36.4)	1 (33.3)
Non Complete Response / Non Progressive Disease	2 (5.4)	0	0	0	1 (9.1)	1 (9.1)	0
Progressive Disease	8 (21.6)	0	2 (66.7)	0	3 (27.3)	2 (18.2)	1 (33.3)
Not Evaluable	1 (2.7)	0	0	0	0	0	1 (33.3)
Confirmed and Unconfirmed							
Complete Response	0	0	0	0	0	0	0
Partial Response	11 (29.7)	0	0	3 (50.0)	0	6 (54.5)	2 (66.7)
Stable Disease	16 (43.2)	3 (100)	1 (33.3)	3 (50.0)	7 (63.6)	2 (18.2)	0
Non Complete Response / Non Progressive Disease	2 (5.4)	0	0	0	1 (9.1)	1 (9.1)	0
Progressive Disease	8 (21.6)	0	2 (66.7)	0	3 (27.3)	2 (18.2)	1 (33.3)
Not Evaluable	0	0	0	0	0	0	0

Table 15: Secondary Efficacy Parameter 2 Best Overall Tumour Response. Part I - Breast Cancer Patients (Full Analysis Population)

All Breast Cancer Patients

Best Overall Tumour Response	Part I Total N=25	Part I SYD985 Dose Level 0.3 mg/kg N=2	0.6 mg/kg N=1	1.2 mg/kg N=5	1.5 mg/kg N=8	1.8 mg/kg N=7	2.4 mg/kg N=2
Confirmed [1]							
Complete Response	0	0	0	0	0	0	0
Partial Response	6 (24.0)	0	0	2 (40.0)	0	4 (57.1)	0
Stable Disease	13 (52.0)	2 (100)	0	3 (60.0)	5 (62.5)	2 (28.6)	1 (50.0)
Non Complete Response / Non Progressive Disease	2 (8.0)	0	0	0	1 (12.5)	1 (14.3)	0
Progressive Disease	3 (12.0)	0	1 (100)	0	2 (25.0)	0	0
Not Evaluable	1 (4.0)	0	0	0	0	0	1 (50.0)
Confirmed and Unconfirmed							
Complete Response	0	0	0	0	0	0	0
Partial Response	10 (40.0)	0	0	3 (60.0)	0	5 (71.4)	2 (100)
Stable Disease	10 (40.0)	2 (100)	0	2 (40.0)	5 (62.5)	1 (14.3)	0
Non Complete Response / Non Progressive Disease	2 (8.0)	0	0	0	1 (12.5)	1 (14.3)	0
Progressive Disease	3 (12.0)	0	1 (100)	0	2 (25.0)	0	0
Not Evaluable	0	0	0	0	0	0	0

[1] A confirmed response is defined as the same or better response recorded >=28 days later
Note: Not Evaluable includes missing responses or no post-baseline response.
Listing Source: 16.2.4.3.1.1, 16.2.6.1
Program Name: t-14-02-02-02-02.sas Table Generation: 31OCT2019 11:32

Part II

Table 16: Secondary Efficacy Parameter Best Overall Tumour Response. Part II – Full Analysis Population

Best Overall Tumor Response	Part II Cohort Total N=141 n (%)	A N=49 n (%)	A1 N=16 n (%)	A2 N=17 n (%)	A3 N=16 n (%)	B N=32 n (%)	C N=15 n (%)	D N=16 n (%)	E N=16 n (%)	F N=13 n (%)
Complete Response	0	0	0	0	0	0	0	0	0	0
Partial Response (confirmed and unconfirmed)	41 (29.1)	16 (32.7)	6 (37.5)	6 (35.3)	4 (25.0)	9 (28.1)	6 (40.0)	1 (6.3)	4 (25.0)	5 (38.5)
Stable Disease	75 (53.2)	30 (61.2)	10 (62.5)	11 (64.7)	9 (56.3)	16 (50.0)	5 (33.3)	10 (62.5)	8 (50.0)	6 (46.2)
Non-Complete Response / Non-Progressive Disease	1 (0.7)	1 (2.0)	0	0	1 (6.3)	0	0	0	0	0
Progressive Disease	24 (17.0)	2 (4.1)	0	0	2 (12.5)	7 (21.9)	4 (26.7)	5 (31.3)	4 (25.0)	2 (15.4)
Not Evaluable	0	0	0	0	0	0	0	0	0	0

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; n = number of patients in specified category; N = total number of patients.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer; Cohort C = HER2-low, HR-negative breast cancer;
Cohort D = gastric cancer; Cohort E = urothelial cancer; Cohort F = endometrial cancer.
Source: Table 14.2.2.2.3

Progression-Free Survival

Part I (solid tumours of any origin)

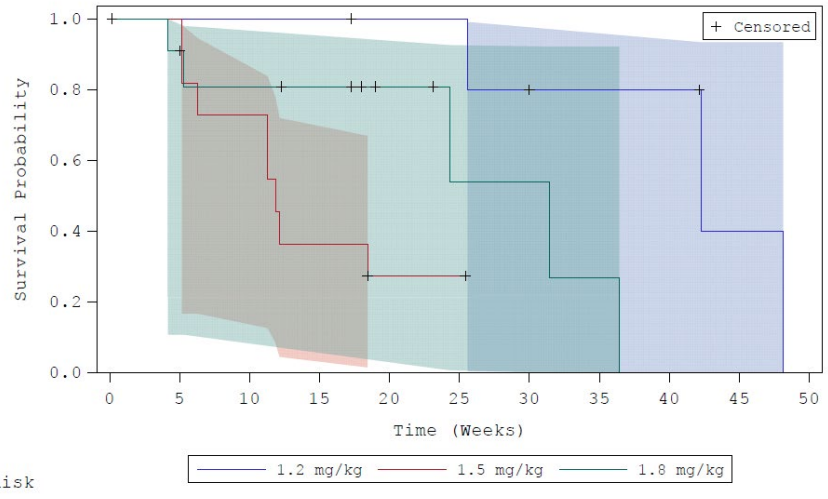
A total of 14 patients (35.9%) did not die, nor did their disease progress during the study (up to and including the 30-day follow-up). The Kaplan-Meier estimate of the median duration of PFS was 18.4 weeks (95% CI: 11.86; 31.43) and was highest for the 1.2 mg/kg dose (42.3 weeks; 95% CI: 25.57; 48.14).

Table 17: Secondary Efficacy Parameter 6 Progression Free Survival (PFS). Part I (Safety Population)

		Part I SYD985 Dose Level		
PFS	Part I Total N=39	0.3 mg/kg N=3	0.6 mg/kg N=3	1.2 mg/kg N=6
Progressed (Event)	24 (61.5%)	3 (100%)	3 (100%)	3 (50.0%)
Died (Event)	1 (2.6%)	0	0	0
Censored	14 (35.9%)	0	0	3 (50.0%)
Kaplan Meier Estimate of PFS (Weeks)				
1st Quartile (95% CI)	11.3 (5.14, 12.00)	12.0 (12.00, 17.29)	5.0 (5.00, 12.00)	42.3 (25.57, 48.14)
Median (95% CI)	18.4 (11.86, 31.43)	12.0 (12.00, 17.29)	5.4 (5.00, 12.00)	42.3 (25.57, 48.14)
3rd Quartile (95% CI)	36.4 (24.29, 48.14)	17.3 (12.00, 17.29)	12.0 (5.00, 12.00)	48.1 (25.57, 48.14)
Kaplan Meier Estimate of PFS (Months)				
1st Quartile (95% CI)	2.6 (1.18, 2.75)	2.8 (2.75, 3.97)	1.1 (1.15, 2.75)	9.7 (5.87, 11.05)
Median (95% CI)	4.2 (2.72, 7.21)	2.8 (2.75, 3.97)	1.2 (1.15, 2.75)	9.7 (5.87, 11.05)
3rd Quartile (95% CI)	8.4 (5.57, 11.05)	4.0 (2.75, 3.97)	2.8 (1.15, 2.75)	11.0 (5.87, 11.05)

		Part I SYD985 Dose Level		
PFS	Part I Total N=39	1.5 mg/kg N=12	1.8 mg/kg N=12	2.4 mg/kg N=3
Progressed (Event)	24 (61.5%)	8 (66.7%)	5 (41.7%)	2 (66.7%)
Died (Event)	1 (2.6%)	0	0	1 (33.3%)
Censored	14 (35.9%)	4 (33.3%)	7 (58.3%)	0
Kaplan Meier Estimate of PFS (Weeks)				
1st Quartile (95% CI)	11.3 (5.14, 12.00)	6.3 (5.14, 11.86)	24.3 (4.14, 31.43)	5.4 (5.43, 24.00)
Median (95% CI)	18.4 (11.86, 31.43)	11.9 (5.14, -)	31.4 (5.29, 36.43)	10.0 (5.43, 24.00)
3rd Quartile (95% CI)	36.4 (24.29, 48.14)	- (11.29, -)	36.4 (24.29, 36.43)	24.0 (5.43, 24.00)
Kaplan Meier Estimate of PFS (Months)				
1st Quartile (95% CI)	2.6 (1.18, 2.75)	1.4 (1.18, 2.72)	5.6 (0.95, 7.21)	1.2 (1.25, 5.51)
Median (95% CI)	4.2 (2.72, 7.21)	2.7 (1.18, -)	7.2 (1.21, 8.36)	2.3 (1.25, 5.51)
3rd Quartile (95% CI)	8.4 (5.57, 11.05)	- (2.59, -)	8.4 (5.57, 8.36)	5.5 (1.25, 5.51)

Figure 7: Secondary Efficacy Parameter 6 Kaplan Meier Plot of Progression Free Survival (PFS). Part I (Safety Population)



At Risk											
1.2 mg/kg	6	6	6	6	5	5	4	3	3	1	0
1.5 mg/kg	12	11	8	4	1	1	0	0	0	0	0
1.8 mg/kg	12	10	8	7	4	2	2	1	0	0	0

Note: PFS is defined as the duration from start of the treatment to disease progression or death (regardless of cause of death), whichever is earlier (including the 30 day follow up). If the patient does not have a documented date of progression or death, or death or progression is after two or more missed assessment, PFS will be censored at the date of the last adequate assessment. 95% Hall-Wellner confidence bands included.
Listing Source: 16.2.6.2.5.1
Program Name: f-14-02-02-06-07.sas Figure Generation: 14NOV2019 9:34

Part II

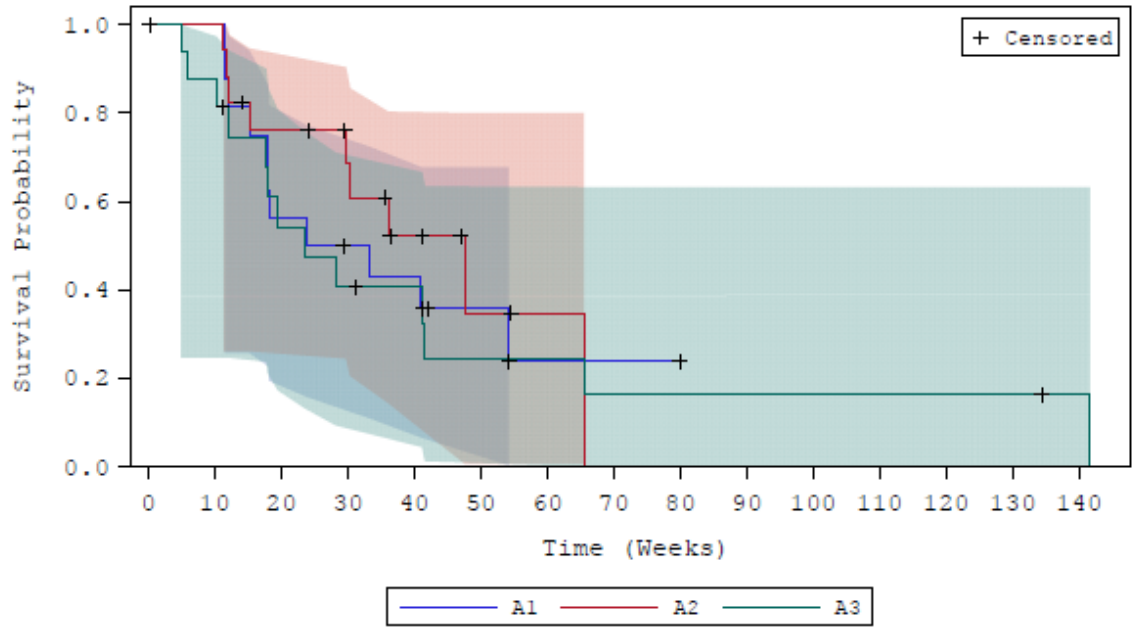
A total of 51 patients (34.9%) did not die, nor did their disease progress during the study (up to and including the 30-day follow-up). The Kaplan-Meier estimate of the median duration of PFS was 21.1 weeks (95% CI: 17.71; 24.00) and was highest for Cohort A2 (47.6 weeks; 95% CI: 15.14; 65.43) *versus* Cohort A1 (28.6 weeks; 95% CI: 15.14; NE) and Cohort A3 (23.4 weeks; 95% CI: 12.14; 41.57).

Table 18: Kaplan-Meier Estimate of Progression-Free Survival (Weeks). Part II – Safety Population

	Part II Cohort									
	Total N=146	A N=50	A1 N=17	A2 N=17	A3 N=16	B N=32	C N=17	D N=17	E N=16	F N=14
Median 95% CI	21.1 17.71, 24.00	33.3 18.14, 47.57	28.6 15.14, -	47.6 15.14, 65.43	23.4 12.14, 41.57	17.4 10.43, 22.29	21.1 5.29, -	14.0 7.00, 23.14	17.7 5.71, 53.29	18.6 10.43, 26.71

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; N = total number of patients.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer;
Cohort C = HER2-low, HR-negative breast cancer; Cohort D = gastric cancer; Cohort E = urothelial cancer;
Cohort F = endometrial cancer.
Source: Table 14.2.2.6.3

Figure 8: Secondary Efficacy Parameter 6 Kaplan Meier Plot of Progression Free Survival (PFS). Part II (Safety Population)



At Risk

A1	17	16	16	13	9	8	7	6	6	3	3	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
A2	17	17	17	13	12	11	9	8	5	4	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A3	16	15	14	11	8	7	6	5	5	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	1	1	0

Note: PFS is defined as the duration from start of the treatment to disease progression or death (regardless of cause of death), whichever is earlier. If the patient does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.
Listing Source: 16.2.6.2.5.1
Program Name: f-14-02-02-06-09.sas Figure Generation: 14NOV2019 9:41

Safety

Extent of exposure

Part I (solid tumours of any origin)

A total of 39 patients received at least 1 dose of SYD985. The median number of cycles that patients started was 4.0; the number ranged from 1 to 16 and the mean number of cycles was 5.3. The number of cycles was higher in the 1.2 mg/kg group (median 10.0 cycles) than in any of the other treatment groups (medians between 2.0 cycles and 5.5 cycles) as well as total dose per patient. The duration of treatment for all patients with breast cancer patients was higher in the 1.2 mg/kg group.

Doses were delayed at least once for 13 patients (33.3%). The incidence was greatest in the 1.2 mg/kg group (5 patients; 83.3%), which was the group with the largest number of cycles. Reasons were decreased LVEF ('no AE reported'), treatment holiday, hospitalisation for gamma knife treatment, and AEs. Proportions of dose reductions were similar between 1.2mg/kg, 1.8 mg/kg and 2.4 mg/kg.

Table 30: Exposure Duration, Total Dose of SYD985 Administered, Dose Delays, and Dose Reductions. Part I - Safety Population

	Part I SYD985 Dose Level						
	Total N=39	**0.3 mg/kg N=3**	**0.6 mg/kg N=3**	**1.2 mg/kg N=6**	**1.5 mg/kg N=12**	**1.8 mg/kg N=12**	**2.4 mg/kg N=3**
Exposure Duration (weeks)[a]							
n	39	3	3	6	12	12	3
Mean	17.16	14.14	8.14	34.60	11.95	17.65	13.24
Standard Deviation	11.227	3.464	3.464	11.087	5.683	10.047	9.807
Median	15.14	12.14	6.14	35.07	12.36	18.14	9.14
Minimum/Maximum	3.1/49.1	12.1/18.1	6.1/12.1	20.1/49.1	3.1/22.6	3.1/33.4	6.1/24.4
Total Dose (mg)							
n	39	3	3	6	12	12	3
Mean	480.5	111.2	105.5	945.8	385.4	526.4	490.8
Standard Deviation	315.88	46.11	48.73	367.69	179.03	208.34	78.54
Median	465.0	99.6	94.0	905.5	404.3	559.5	505.5
Minimum/Maximum	64/1387	72/162	64/159	527/1387	118/648	156/900	406/561
Dose Delayed, n (%)							
Yes	13 (33.3)	0	0	5 (83.3)	2 (16.7)	5 (41.7)	1 (33.3)
No	26 (66.7)	3 (100)	3 (100)	1 (16.7)	10 (83.3)	7 (58.3)	2 (66.7)
No. Dose Delays							
0	26 (66.7)	3 (100)	3 (100)	1 (16.7)	10 (83.3)	7 (58.3)	2 (66.7)
1	8 (20.5)	0	0	3 (50.0)	2 (16.7)	3 (25.0)	0
2	2 (5.1)	0	0	1 (16.7)	0	1 (8.3)	0
> 2	3 (7.7)	0	0	1 (16.7)	0	1 (8.3)	1 (33.3)
Dose Reduced, n (%)							
Yes	7 (17.9)	0	0	2 (33.3)	0	4 (33.3)	1 (33.3)
No	32 (82.1)	3 (100)	3 (100)	4 (66.7)	12 (100)	8 (66.7)	2 (66.7)
No. Dose Reductions							
0	32 (82.1)	3 (100)	3 (100)	4 (66.7)	12 (100)	8 (66.7)	2 (66.7)
1	6 (15.4)	0	0	2 (33.3)	0	4 (33.3)	0
2	1 (2.6)	0	0	0	0	0	1 (33.3)
> 2	0	0	0	0	0	0	0

n = number of patients in specified category; N = total number of patients.
[a] Treatment duration was calculated as [(last treatment date – first treatment date) + 22] / 7.
Source: Table 14.3.1.1

Part II

A total of 146 patients received at least 1 dose of 1.2 mg/kg SYD985. Median exposure durations were similar between cohort A1 and A2. Cohort A3 were less exposed.

For 61 patients (41.8%), there was an unplanned dose delay at least once with an incidence of 64.7% in Cohort A1, 64.7% in Cohort A2, and 31.3% in Cohort A3. The most frequently reported reason was AEs. For 30 patients (20.5%), there was an unplanned dose reduction at some point during the study; this occurred for 41.2% of patients in Cohort A1, 5.9% of patients in Cohort A2 and 18.8% of patients in Cohort A3).

Table 19: Exposure Duration, Total Dose of SYD985 Administered, Dose Delays, and Dose Reductions. Part II - Safety Population

	Part II Cohort									
	Total N=146	**A N=50**	**A1 N=17**	**A2 N=17**	**A3 N=16**	**B N=32**	**C N=17**	**D N=17**	**E N=16**	**F N=14**
Exposure Duration (weeks)[a]										
n	146	50	17	17	16	32	17	17	16	14
Mean	21.91	33.20	29.61	33.26	36.95	16.29	14.33	14.13	17.71	17.88
Standard Deviation	19.914	27.370	19.621	16.823	41.293	9.919	9.470	9.153	13.920	12.918
Median	17.36	28.14	27.14	32.29	20.93	13.50	12.14	12.14	1516.64	16.64
Minimum/Maximum	3.1/139.3	3.1/139.3	3.1/80.1	12.1/66.1	6.1/139.3	3.1/45.0	3.1/31.1	3.1/30.3	3.1/55.6	3.1/44.1
Total Dose (mg)										
n	146	50	17	17	16	32	17	17	16	14
Mean	500.5	634.7	653.1	656.0	592.6	409.8	407.4	439.2	491.2	426.4
Standard Deviation	315.55	333.47	349.25	308.11	359.30	256.70	285.11	270.29	371.09	271.42
Median	450.9	556.4	651.0	578.0	469.8	322.4	484.2	351.5	460.3	423.0
Minimum/Maximum	51/1479	78/1369	78/1322	252/1255	156/1369	82/1130	59/904	90/935	76/1479	51/854
Dose Delayed, n (%)										
Yes	61 (41.8)	27 (54.0)	11 (64.7)	11 (64.7)	5 (31.3)	15 (46.9)	6 (35.3)	5 (29.4)	3 (18.8)	5 (35.7)
No	85 (58.2)	23 (46.0)	6 (35.3)	6 (35.3)	11 (68.8)	17 (53.1)	11 (64.7)	12 (70.6)	13 (81.3)	9 (64.3)
No. Dose Delays										
0	85 (58.2)	23 (46.0)	6 (35.3)	6 (35.3)	11 (68.8)	17 (53.1)	11 (64.7)	12 (70.6)	13 (81.3)	9 (64.3)
1	35 (24.0)	13 (26.0)	4 (23.5)	7 (41.2)	2 (12.5)	9 (28.1)	4 (23.5)	4 (23.5)	2 (12.5)	3 (21.4)
2	16 (11.0)	7 (14.0)	4 (23.5)	2 (11.8)	1 (6.3)	5 (15.6)	2 (11.8)	1 (5.9)	0	1 (7.1)
> 2	10 (6.8)	7 (14.0)	3 (17.6)	2 (11.8)	2 (12.5)	1 (3.1)	0	0	1 (6.3)	1 (7.1)
Dose Reduced, n (%)										
Yes	30 (20.5)	11 (22.0)	7 (41.2)	1 (5.9)	3 (18.8)	8 (25.0)	2 (11.8)	2 (11.8)	4(25.0)	3 (21.4)
No	116 (79.5)	39 (78.0)	10 (58.8)	16 (94.1)	13 (81.3)	24 (75.0)	15 (88.2)	15 (88.2)	12 (75.0)	11 (78.6)
No. Dose Reductions										
0	116 (79.5)	39 (78.0)	10 (58.8)	16 (94.1)	13 (81.3)	24 (75.0)	15 (88.2)	15 (88.2)	12 (75.0)	11 (78.6)
1	27 (18.5)	9 (18.0)	6 (35.3)	1 (5.9)	2 (12.5)	7 (21.9)	2 (11.8)	2 (11.8)	4 (25.0)	3 (21.4)
2	3 (2.1)	2 (4.0)	1 (5.9)	0	1 (6.3)	1 (3.1)	0	0	0	0
> 2	0	0	0	0	0	0	0	0	0	0

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; n = number of patients in specified category; N = total number of patients.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer;
Cohort C = HER2-low, HR-negative breast cancer; Cohort D = gastric cancer; Cohort E = urothelial cancer;
Cohort F = endometrial cancer.
[a] Treatment duration was calculated as [(last treatment date – first treatment date) + 22] / 7.
Source: Table 14.3.1.1

Adverse events

Part I (solid tumours of any origin)

Table 202: Treatment-Emergent Adverse Events Overall Summary. Part I - Safety Population

	Part I SYD985 Dose Level																				
	Total N=39			0.3 mg/kg N=3			0.6 mg/kg N=3			1.2 mg/kg N=6			1.5 mg/kg N=12			1.8 mg/kg N=12			2.4 mg/kg N=3		
Parameter	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
TEAEs	39	100	557	3	100	12	3	100	36	6	100	162	12	100	149	12	100	152	3	100	46
Serious TEAEs	18	46.2	25	0	0.0	0	1	33.3	1	2	33.3	4	7	58.3	11	5	41.7	6	3	100	3
Treatment-Related TEAEs	38	97.4	351	3	100	8	3	100	13	6	100	113	11	91.7	92	12	100	92	3	100	33
TEAEs Leading to Drug Withdrawal	11	28.2	18	0	0.0	0	0	0.0	0	3	50.0	7	3	25.0	6	3	25.0	3	2	66.7	2
TEAEs Leading to Death	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1
Dose-Limiting Toxicity	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1

E = number of events; n = number of patients in specified category; N = total number of patients; TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.1

Table 213: Drug-Related Treatment-Emergent Adverse Events With a Grade ≥ 3. Part I - Safety Population

	Part I SYD985 Dose Level																				
	Total N=39			0.3 mg/kg N=3			0.6 mg/kg N=3			1.2 mg/kg N=6			1.5 mg/kg N=12			1.8 mg/kg N=12			2.4 mg/kg N=3		
SYSTEM ORGAN CLASS Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Patients With at Least 1 Related TEAE With a Toxicity Grade ≥ 3	13	33.3	22	0	0.0	0	0	0.0	0	5	83.3	8	2	16.7	4	3	25.0	6	3	100	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4	10.3	4	0	0.0	0	0	0.0	0	2	33.3	2	0	0.0	0	1	8.3	1	1	33.3	1
Fatigue	2	5.1	2	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	1	8.3	1	0	0.0	0
Asthenia	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
Injection site reaction	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1
INVESTIGATIONS	3	7.7	6	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	2	16.7	5	0	0.0	0
Ejection fraction decreased	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
Neutrophil count decreased	1	2.6	2	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	2	0	0.0	0
Platelet count decreased	1	2.6	3	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	3	0	0.0	0
EYE DISORDERS	3	7.7	5	0	0.0	0	0	0.0	0	1	16.7	1	1	8.3	3	0	0.0	0	1	33.3	1
Keratitis	3	7.7	3	0	0.0	0	0	0.0	0	1	16.7	1	1	8.3	1	0	0.0	0	1	33.3	1
Conjunctivitis	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	1	0	0.0	0	0	0.0	0
Episcleritis	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	1	0	0.0	0	0	0.0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	5.1	2	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	1	0	0.0	0	1	33.3	1
Neutropenia	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1
Anaemia	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	1	8.3	1	0	0.0	0	0	0.0	0
CARDIAC DISORDERS	1	2.6	2	0	0.0	0	0	0.0	0	1	16.7	2	0	0.0	0	0	0.0	0	0	0.0	0
Pericardial effusion	1	2.6	2	0	0.0	0	0	0.0	0	1	16.7	2	0	0.0	0	0	0.0	0	0	0.0	0
GASTROINTESTINAL DISORDERS	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
Stomatitis	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
METABOLISM AND NUTRITION DISORDERS	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
Decreased appetite	1	2.6	1	0	0.0	0	0	0.0	0	1	16.7	1	0	0.0	0	0	0.0	0	0	0.0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1
Pneumonitis	1	2.6	1	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	1	33.3	1

E = number of events; n = number of patients in specified category; N = total number of patients; TEAE = treatment-emergent adverse event.
Source: Table 14.3.2.7.2

Part II

Table 22: Treatment-Emergent Adverse Events Overall Summary. Part II - Safety Population

	Part II Cohort																			
	Total N=146		A N=50		A1 N=17		A2 N=17		A3 N=16		B N=32		C N=17		D N=17		E N=16		F N=14	
Parameter	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
TEAEs	146 (100)	2553	50 (100)	1022	17 (100)	345	17 (100)	329	16 (100)	348	32 (100)	571	17 (100)	306	17 (100)	210	16 (100)	255	14 (100)	189
Serious TEAEs	59 (40.4)	99	21 (42.0)	35	7 (41.2)	10	7 (41.2)	13	7 (43.8)	12	12 (37.5)	19	5 (29.4)	6	8 (47.1)	15	5 (31.3)	13	8 (57.1)	11
Treatment-Related TEAEs	139 (95.2)	1330	49 (98.0)	583	16 (94.1)	214	17 (100)	159	16 (100)	210	32 (100)	275	15 (88.2)	172	15 (88.2)	92	16 (100)	128	12 (85.7)	80
TEAEs Leading to Drug Withdrawal	29 (19.9)	49	10 (20.0)	16	5 (29.4)	7	3 (17.6)	3	2 (12.5)	6	7 (21.9)	9	2 (11.8)	5	3 (17.6)	10	3 (18.8)	4	4 (28.6)	5
TEAEs Leading to Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

E = number of events; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; n = number of patients in specified category; N = total number of patients; TEAE = treatment-emergent adverse event.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer; Cohort C = HER2-low, HR-negative breast cancer; Cohort D = gastric cancer; Cohort E = urothelial cancer; Cohort F = endometrial cancer.
Source: Table 14.3.2.1

Table 23: Drug-Related Treatment-Emergent Adverse Events With a Grade ≥ 3 with Incidence > 2.0% Overall. Part II - Safety Population

	Part II Cohort																			
	Total N=146		A N=50		A1 N=17		A2 N=17		A3 N=16		B N=32		C N=17		D N=17		E N=16		F N=14	
SYSTEM ORGAN CLASS Preferred Term	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Patients With at Least One Related TEAE With a Toxicity Grade ≥ 3	51 (34.9)	86	15 (30.0)	34	4 (23.5)	5	7 (41.2)	11	4 (25.0)	18	11 (34.4)	17	8 (47.1)	11	6 (35.3)	6	8 (50.0)	14	3 (21.4)	4
INVESTIGATIONS	13 (8.9)	17	3 (6.0)	4	1 (5.9)	1	1 (5.9)	1	1 (6.3)	2	2 (6.3)	4	2 (11.8)	2	2 (11.8)	2	3 (18.8)	4	1 (7.1)	1
Lymphocyte count decreased	3 (2.1)	4	1 (2.0)	1	0	0	1 (5.9)	1	0	0	0	0	0	0	0	0	2 (12.5)	3	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	13 (8.9)	29	5 (10.0)	18	2 (11.8)	3	2 (11.8)	5	1 (6.3)	10	1 (3.1)	1	4 (23.5)	6	1 (5.9)	1	2 (12.5)	3	0	0
Neutropenia	9 (6.2)	23	5 (10.0)	18	2 (11.8)	3	2 (11.8)	5	1 (6.3)	10	1 (3.1)	1	3 (17.6)	4	0	0	0	0	0	0
EYE DISORDERS	10 (6.8)	11	4 (8.0)	5	1 (5.9)	1	2 (11.8)	2	1 (6.3)	2	4 (12.5)	4	0	0	1 (5.9)	1	1 (6.3)	1	0	0
Conjunctivitis	4 (2.7)	4	2 (4.0)	2	0	0	1 (5.9)	1	1 (6.3)	1	2 (6.3)	2	0	0	0	0	0	0	0	0
Keratitis	3 (2.1)	3	2 (4.0)	2	1 (5.9)	1	1 (5.9)	1	0	0	1 (3.1)	1	0	0	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (3.4)	6	1 (2.0)	2	0	0	1 (5.9)	2	0	0	2 (6.3)	2	1 (5.9)	1	0	0	1 (6.3)	1	0	0
Fatigue	5 (3.4)	6	1 (2.0)	2	0	0	1 (5.9)	2	0	0	2 (6.3)	2	1 (5.9)	1	0	0	1 (6.3)	1	0	0
CARDIAC DISORDERS	4 (2.7)	4	2 (4.0)	2	0	0	0	0	2 (12.5)	2	0	0	1 (5.9)	1	1 (5.9)	1	0	0	0	0
Pericardial effusion	3 (2.1)	3	2 (4.0)	2	0	0	0	0	2 (12.5)	2	0	0	1 (5.9)	1	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (2.1)	5	2 (4.0)	3	0	0	1 (5.9)	1	1 (6.3)	2	0	0	0	0	0	0	1 (6.3)	2	0	0

E = number of events; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; n = number of patients in specified category; N = total number of patients; TEAE = treatment-emergent adverse event.
Cohort A = HER2-positive breast cancer; Cohort B = HER2-low, HR-positive breast cancer; Cohort C = HER2-low, HR-negative breast cancer; Cohort D = gastric cancer; Cohort E = urothelial cancer; Cohort F = endometrial cancer.
Source: Table 14.3.2.7.2

3.3.4.2. Main study

SYD985.002 (TULIP)

Multicentre, phase III, open-label, randomized clinical trial comparing the efficacy and safety of the antibody-drug conjugate trastuzumab duocarmazine (SYD985) to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer.

Methods

Study Participants

Inclusion Criteria

Any patient must meet the following inclusion criteria:

1. Female patients, age ≥ 18 years old at the time of signing informed consent;

2. Patients with histologically-confirmed, unresectable locally advanced or metastatic breast cancer;

3. Patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment for locally advanced or metastatic disease;

4. HER2-positive tumour status according to the ASCO-CAP guidelines (defined as a 3+ score on immunohistochemistry (IHC) and/or positive by in situ hybridisation (ISH)) confirmed by the central laboratory;

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

6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

7. Estimated life expectancy > 12 weeks at randomisation;

8. Adequate organ function, evidenced by the following (local) laboratory results:

   – Absolute neutrophil count ≥ 1.5 x 10^9/L;

   – Platelet count ≥ 100 x 10^9/L;

   – Haemoglobin ≥ 9.0 g/dL;

   – Total bilirubin ≤ 1.5 x the upper limit of normal (ULN);

   – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases);

   – Serum creatinine ≤ 1.5 x ULN;

9. For women of childbearing potential two methods of effective contraception must be used during the study and up to 6 months after last study treatment. This is not required in case the patient or sole partner is surgically sterilised or in case the patient truly abstains from sexual activity.

Exclusion Criteria

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

1. Having been treated with:

    a. SYD985 at any time;

    b. Anthracycline treatment within 12 weeks prior to randomisation;

    c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to randomisation;

    d. Radiotherapy within 2 weeks prior to randomisation;

    e. Hormone therapy within 1 week prior to randomisation;

    The patient must have sufficiently recovered from any treatment-related toxicities to NCI CTCAE Grade ≤ 1 (except for toxicities not considered a safety risk for the patient at the investigator's discretion);

2. History of infusion-related reactions and/or hypersensitivity to trastuzumab, (ado-)trastuzumab emtansine or excipients of the study drug which led to permanent discontinuation of the treatment;

3. History of keratitis;

4. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening;

5. Left ventricular ejection fraction (LVEF) < 50% as assessed by either echocardiography or multigated acquisition (MUGA) scan at screening, or a history of clinically significant decrease in LVEF during previous treatment with trastuzumab or (ado-)trastuzumab emtansine leading to permanent discontinuation of treatment;

6. Cardiac troponin value above the ULN (local laboratory) at screening;

7. History (within 6 months prior to randomisation) of clinically significant cardiovascular disease such as unstable angina, congestive heart failure (CHF), myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;

8. Untreated brain metastases, symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, treatment for brain metastases within 8 weeks prior to randomisation. Patients with prior treatment of brain metastasis must have evidence of disease stability on baseline brain imaging as compared to historical brain imaging;

9. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;

10. Known active Hepatitis B or C infection;

11. Major surgery within 4 weeks prior to randomisation;

12. Pregnancy or lactation;

13. Other condition, which in the opinion of the investigator, would compromise the safety of the patient or the patient's ability to complete the study.

Treatments

SYD985 1.2 mg/kg was administered every 3 weeks (±3 days) via intravenous (IV) infusion over 60 minutes (±10 minutes) for the first infusion; subsequent infusions were allowed to be given over 30 minutes.

If a patient needs a dose reduction of SYD985 the dose should be reduced from 1.2 mg/kg to 0.9 mg/kg. Patients on the 0.9 mg/kg dose who develop an AE necessitating further dose reductions should be reduced to 0.6 mg/kg (introduced with Amendment 3, Version 4.0, dated 11 September 2018). Patients on the 0.6 mg/kg dose who develop an AE necessitating further dose reductions should be discontinued from treatment. Dose escalation is not allowed after a dose reduction.

Physician's choice therapy options included:

- Option 1: lapatinib + capecitabine
- Option 2: trastuzumab + capecitabine
- Option 3: trastuzumab + vinorelbine
- Option 4: trastuzumab + eribulin

The physician's choice therapy was to be administered in accordance with labelling and local clinical practice.

Objectives

Primary Objectives

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

Secondary Objectives

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

Exploratory Objectives

The other objectives of this study are as follows:

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

Outcomes/endpoints

Primary Efficacy Endpoint

PFS based on blinded ICR of tumour assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS was defined as the time from the date of randomisation to the date

of first documented ICR-assessed disease progression according to RECIST v1.1 or death due to any cause (whichever occurred earlier)

Secondary Efficacy Endpoints

- OS: defined as the time from the date of randomisation to the date of death due to any cause
- ORR: defined as the proportion of patients with ICR-assessed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1
- Investigator-assessed PFS: defined as the time from the date of randomisation to the date of first documented investigator-assessed disease progression according to RECIST v1.1 or death due to any cause (whichever occurred earlier)
- PROs for health-related QoL collected from the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire–core (EORTC QLQ-C30) along with the EORTC disease-specific breast cancer QoL questionnaire (EORTC QLQ-BR23)

Exploratory Efficacy Endpoints

- TTR: defined as the time between the date of randomisation until first documented response (CR or PR) according to RECIST v1.1
- DOR only applied to patients whose best overall response was CR or PR according to RECIST v1.1. The start date was the date of first documented response (CR or PR), and the end date was the date defined as first documented disease progression or death from any cause (whichever occurred first)
- CBR was defined as the proportion of patients with CR, PR, or stable disease (stable disease for ≥6 months) for patients with measurable disease, or with CR or non-CR/non-PD (non-CR/non-PD for ≥6 months) for patients with non-measurable disease
- PK parameters for total SYD985 (including SYD985 with a drug-to-antibody ratio [DAR] ≥0), conjugated SYD985 with DAR ≥1, and SYD986, including but not limited to area under the curve (AUC), maximum blood plasma concentration (Cmax), minimum blood plasma concentration (Cmin), drug clearance (CL), volume of distribution (Vz), and terminal half-life, were reported as data allowed; the inter-patient variability was also assessed
- The formation of SYD985 ADAs was assessed. Results of this analysis were provided in a separate report
- Exploratory analysis or modelling techniques were used to investigate the relationship between SYD985 exposure and safety/efficacy parameters (e.g., SYD985-related toxicity, PFS, and/or OS) if data allowed.

Sample size

From the applicant perspective, the most relevant comparable trial prior to the start of the SYD985 phase III trial was a trial including patients with pretreated HER2-positive locally advanced or metastatic breast cancer in which trastuzumab emtansine was compared to physician's choice (TH3RESA trial, Krop et al., 2014). In that trial the median (95% CI) PFS in the physician's choice group was 3.3 (2.89, 4.14) months. In the years after the TH3RESA trial several HER2-targeting agents have been approved and are increasingly being used, for example: pertuzumab, trastuzumab emtansine and eribulin. Therefore, it was expected that patients included in the SYD985.002 trial, who progressed on these new therapies, would have a prognosis that was, at best, comparable but likely worse (i.e. due to more common and extensive HER2-targeting treatment in prior lines) than the prognosis for patients in the physician's

choice group in the TH3RESA trial. The aim of the SYD985.002 trial was to show an improvement of at least 35% in PFS by SYD985 as compared to contemporary physician's choice; in addition, this was expected to be associated with a gain of at least 1.5 months in PFS. Meeting or exceeding these criteria would also represent a meaningful clinical benefit according to the criteria of the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (Cherny et al., 2015). In order to detect a hazard ratio of 0.65 in PFS, using the log-rank test at 90% power using a two-sides test at a significance level of $p < 0.05$, a total of 256 events would be required. In the initial sample size calculations the following was assumed: 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 an average of 20% drop out in the physician's choice group and 30% in the SYD985 group. This resulted in the assumption that a minimal number of 345 patient would be required. As part of their evaluation, the independent data monitoring committee (DMC) assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size, assuming an average of 30% drop out in the physician's choice group and 40% in the SYD985 group and enrol a total of 423 patients to ensure sufficient power for the primary endpoint analysis. The protocol was amended accordingly following this DMC recommendation (protocol amendment VI, October 2019).

Randomisation and blinding (masking)

This was an open-label study.

Using a computer-generated randomisation list, eligible patients were randomly assigned in a 2:1 ratio to receive SYD985 or physician's choice treatment.

The allocation was stratified for:

- geographical region (Europe and Singapore versus North America),
- the number of prior treatment lines for advanced breast cancer (excluding hormone therapy) (1 or 2 versus more than 2),
- and prior treatment with pertuzumab (yes versus no).

Statistical methods

The efficacy analysis will be performed using the FAS which included all patients who signed an ICF and were randomised. As a measure of sensitivity, efficacy analyses were also performed based on the data in the per protocol set (PPS), which included patients who were administered at least 1 dose of trial medication and who did not have any major protocol deviations. In addition, on the FAS population sensitivity analyses were performed with actual treatment received, without stratification factors, earliest progressive disease (PD) from ICR or local assessment and PD one day after last RECIST. Subgroup analyses by baseline demographics, stratification factors, and key disease characteristics were pre-specified to assess the overall consistency of efficacy results.

The primary endpoint PFS by ICR and secondary endpoints OS and PFS by local assessment were estimated using the Kaplan-Meier method. The comparison of the distributions of PFS and OS between the two treatment groups was performed using a stratified log-rank test at the 2-sided 5% level of significance. A stratified Cox regression analysis was used to estimate the hazard ratio, along with 95% CIs. For ORR, the percentage of patients with a response was summarised by treatment group along with 95% CIs. A Cochran-Mantel-Haenszel test was used to compare the two treatment groups with respect to the ORR at a 2-sided 5% level of significance.

For PROs of QoL the change from baseline in the global health status/QoL scale transformed score was analysed using a mixed model repeated measurement (MMRM) approach.

There was no interim analysis of efficacy in the trial.

Rules for censoring (primary endpoint of PFS) are summarised in the table below.

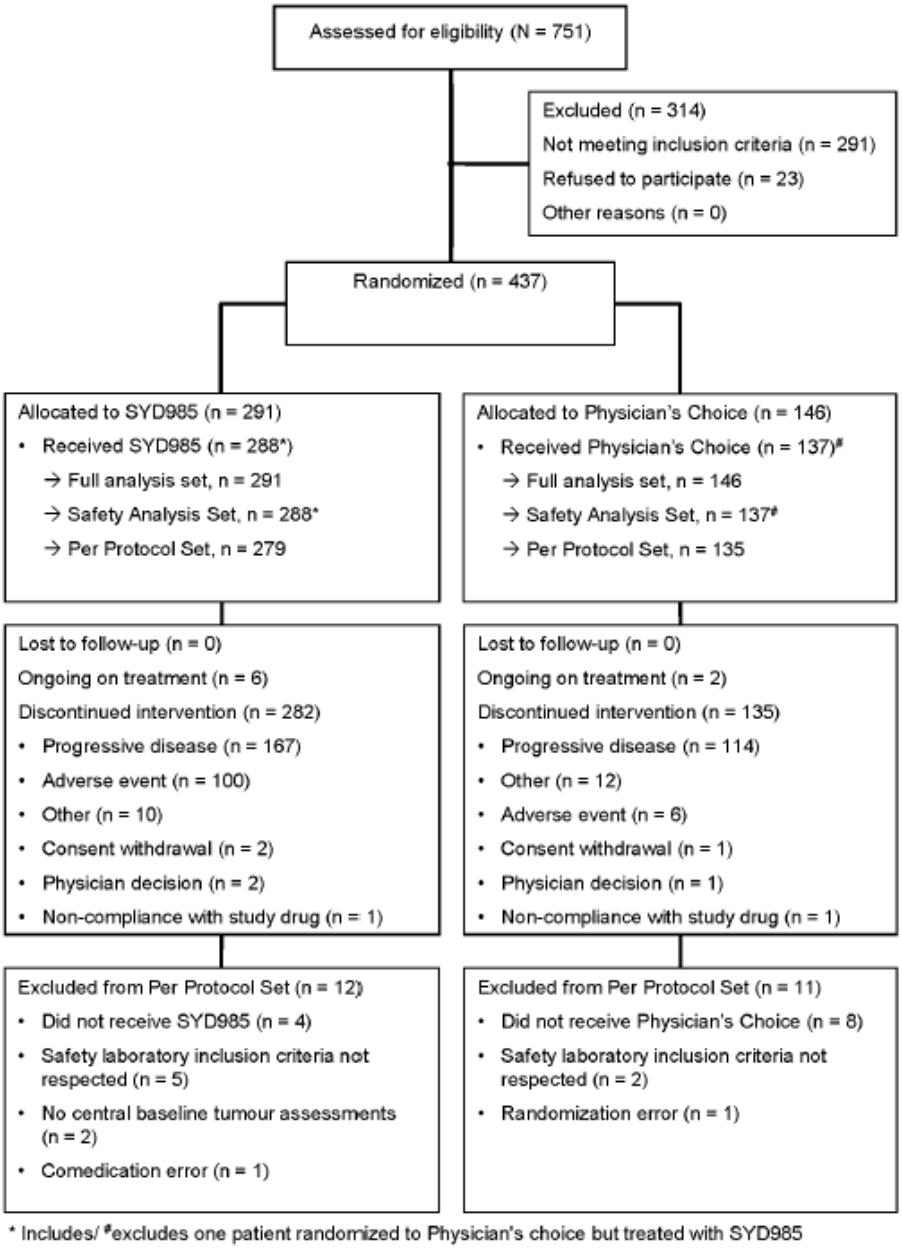
Table 24: Rules for censoring (PFS)

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

Results

Figure 9: Participant flow for trial SYD985.002

Participant flow



Recruitment

The study was initiated the 07 December 2017 (first patient first visit).

Every 3 months after the treatment discontinuation visit, a survival follow-up visit (or phone call) was scheduled. During this visit, data were collected on disease progression, unresolved AEs, new anticancer therapies, and survival. These survival follow-up visits continued until a patient's death, lost to follow-up, or consent withdrawal, whichever came first.

Conduct of the study

Protocol amendments

The original protocol (version 1.0, dated 31 May 2017) was amended 7 times. The trial started under version 2.0 (dated 25 August 2017). Substantial changes made by each amendment starting from Amendment 2, version 3, are described as follows:
Protocol Amendment 2, Version 3.0, dated 09 November 2017:

This substantial amendment was prepared upon request of the regulatory authorities. The flowchart was updated to add pregnancy tests on Day 1 of every cycle and at the treatment discontinuation visit.

- The flowchart was updated to add an ECG assessment at Cycle 3 Day 1.
- A total of 5 protocol sections were updated to reiterate and emphasise the importance to follow the SmPC guidance for patient selection and management in the physician's choice group.
- A section on the benefit/risk ratio was added.
- In relation to cardiotoxicity, it was added that clinically relevant electrolyte disturbances should be corrected.
- The possibility to enable further SYD985 treatment when the study has ended was added.
- The indicated contraception was updated to be aligned with the Clinical Trials Facilitation and Coordination Group recommendations.

Protocol Amendment 3, Version 4.0, dated 11 September 2018:

This substantial amendment was prepared for the following reasons:

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

Protocol Amendment 4, Version 5.0, dated 12 April 2019:

This substantial amendment was prepared for the following reasons:

- Upon request of the DMC, keratitis grade $\geqslant$2 was added as an AESI.
- In consultation with the Steering Committee and the DMC, Section 8.2 was updated to add the possibility to allow rescreening for patients for whom during screening on the brain CT/MRI a previously unknown asymptomatic metastasis was observed.
- Section 11.9 and the flowchart were updated to add the possibility to perform the pregnancy test up to 3 days before Day 1 of a new cycle for practical reasons.
- Section 11.21 and the flowchart were updated to add that the treatment discontinuation visit should be performed before new anticancer treatment was initiated.

Protocol Amendment 5, Version 6.0, dated 24 May 2019:

This substantial amendment was prepared upon request of the regulatory authorities. The changes are summarised below:

- Section 5.5.1 was updated to include additional information on interstitial lung disease/pneumonitis
- In Section 9.5.1.4, dose modifications for interstitial lung disease/pneumonitis were expanded.
- In Section 11.5, oxygen saturation by pulse oximetry was added to the vital sign assessments

at all visits.

Protocol Amendment 6, Version 7.0, dated 22 October 2019:

This substantial amendment was prepared for the following reason:

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

Protocol Amendment 7, Version 8.0, dated 18 January 2021:

This substantial amendment was prepared for the following reasons:

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

Major protocol deviations

Table 25: Major Protocol Deviations – FAS

Number of Patients, n (%)	SYD985 N=291	Physician's Choice N=146	Total N=437
Patients with a major protocol deviation	55 (18.9)	20 (13.7)	75 (17.2)
Total number of major protocol deviations	67	21	88
Deviation category/deviation sub-category			
Adverse events and therapy	20 (6.9)	1 (0.7)	21 (4.8)
SAE not reported within 24-hour timeline	6 (2.1)	0	6 (1.4)
Other	14 (4.8)	1 (0.7)	15 (3.4)
Eligibility criteria	31 (10.7)	16 (11.0)	47 (10.8)
Tumor evaluation scans performed out of window	1 (0.3)	0	1 (0.2)
Violation of exclusion criteria	16 (5.5)	10 (6.8)	26 (5.9)
Violation of inclusion criteria	13 (4.5)	5 (3.4)	18 (4.1)
Other	2 (0.7)	2 (1.4)	4 (0.9)
Informed consent form	3 (1.0)	0	3 (0.7)
Study procedures performed before patient signed consent	3 (1.0)	0	3 (0.7)
Investigational product	3 (1.0)	0	3 (0.7)
Dose discontinuation not per protocol	1 (0.3)	0	1 (0.2)
Dose modification not per protocol	1 (0.3)	0	1 (0.2)
Incorrect dose administered	1 (0.3)	0	1 (0.2)
Laboratory sample	0	1 (0.7)	1 (0.2)
Per protocol laboratory samples not taken during visit	0	1 (0.7)	1 (0.2)
Procedure not per protocol	1 (0.3)	0	1 (0.2)
Missed per protocol procedure other than laboratory sample	1 (0.3)	0	1 (0.2)
Randomization error	2 (0.7)	1 (0.7)	3 (0.7)
Incorrect stratification data entered	2 (0.7)	0	2 (0.5)
Patient not treated with assigned treatment arm	0	1 (0.7)	1 (0.2)
Tumor evaluation	2 (0.7)	0	2 (0.5)
Tumor evaluation scans not performed	1 (0.3)	0	1 (0.2)
Tumor evaluation scans performed out of window	1 (0.3)	0	1 (0.2)
Visit schedule not respected	0	1 (0.7)	1 (0.2)
Visit out of window	0	1 (0.7)	1 (0.2)

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; SAE, serious adverse event.
Cross-reference: Listing 16.2.2.1
Source: Table 14.1.2.1

Baseline data

Table 26: Patient Demographic and Baseline Characteristics – FAS

Characteristic		SYD985 N=291	Physician's Choice N=146	Total N=437
Age (years)	N	291	146	437
	Mean	55.9	57.3	56.4
	SD	11.20	10.97	11.13
	Median	56.0	58.0	56.0
	Min/max	24/84	34/86	24/86
Sex, n (%)	Female	291 (100)	146 (100)	437 (100)
Childbearing potential, n (%)	Yes	64 (22.0)	32 (21.9)	96 (22.0)
	No – postmenopausal	204 (70.1)	105 (71.9)	309 (70.7)
	No – surgically sterilized	23 (7.9)	9 (6.2)	32 (7.3)
Race, n (%)	American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
	Asian	29 (10.0)	17 (11.6)	46 (10.5)
	Black or African American	4 (1.4)	2 (1.4)	6 (1.4)
	White	202 (69.4)	95 (65.1)	297 (68.0)
	Other	1 (0.3)	2 (1.4)	3 (0.7)
	Not disclosed	54 (18.6)	30 (20.5)	84 (19.2)
Ethnicity, n (%)	Hispanic or Latino	11 (3.8)	8 (5.5)	19 (4.3)
	Not Hispanic or Latino	225 (77.3)	103 (70.5)	328 (75.1)
	Not disclosed	55 (18.9)	35 (24.0)	90 (20.6)
BMI	N	288	145	433
	Mean	25.14	25.54	25.28
	SD	5.0	6.1	5.4
	Median	24.26	24.46	24.27
	Min/max	14.5/44.8	13.1/55.3	13.1/55.3

Abbreviations: BMI, body mass index; FAS, full analysis set; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with data available.
Cross-reference: Listing 16.2.4.1
Source: Table 14.1.3.1.1

Table 27: Baseline Disease Characteristics – FAS

Characteristic		SYD985 N=291	Physician's Choice N=146	Total N=437
Time from diagnosis to study entry (years) [1]	n	291	146	437
	Mean	7.1	7.5	7.2
	SD	5.1	5.9	5.4
	Median	5.77	5.80	5.77
	Min/max	0.7/31.3	0.9/30.2	0.7/31.3
Time from locally advanced or metastatic disease diagnosis to study entry (years) [2]	n	291	146	437
	Mean	4.2	4.0	4.2
	SD	2.9	3.4	3.1
	Median	3.60	2.93	3.46
	Min/max	0.0/18.6	0.0/19.5	0.0/19.5
Histological classification, n (%)	Ductal carcinoma	263 (90.4)	128 (87.7)	391 (89.5)
	Lobular carcinoma	7 (2.4)	9 (6.2)	16 (3.7)
	Other	21 (7.2)	9 (6.2)	30 (6.9)
Disease type, n (%)	Locally advanced	18 (6.2)	10 (6.8)	28 (6.4)
	Metastatic	273 (93.8)	136 (93.2)	409 (93.6)
Metastatic sites, n (%)	Bone	138 (47.4)	61 (41.8)	199 (45.5)
	Breast	17 (5.8)	14 (9.6)	31 (7.1)
	Hepatic lobe	95 (32.6)	43 (29.5)	138 (31.6)
	Lung	138 (47.4)	71 (48.6)	209 (47.8)
	Lymph nodes	161 (55.3)	85 (58.2)	246 (56.3)
	Skin	31 (10.7)	24 (16.4)	55 (12.6)
	Other	63 (21.6)	37 (25.3)	100 (22.9)

Visceral disease, n (%)		171 (58.8)	88 (60.3)	259 (59.3)
Non-visceral disease, n (%)		99 (34.0)	49 (33.6)	148 (33.9)
Brain metastases, n (%)	Yes	40 (13.7)	16 (11.0)	56 (12.8)
	No	251 (86.3)	130 (89.0)	381 (87.2)
HR status, n (%) [3]	Positive	159 (54.6)	85 (58.2)	244 (55.8)
	Negative	123 (42.3)	59 (40.4)	182 (41.6)
	Unknown	9 (3.1)	2 (1.4)	11 (2.5)

Abbreviations: FAS, full analysis set; HR, hormone receptor; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with data available.
[1] Calculated in years as informed consent date – diagnosis date + 1/365.25.
[2] Calculated in years as informed consent date – diagnosis date of locally advanced or metastatic disease + 1/365.25.
[3] "Unknown" also included patients with HR status not available.
Cross-reference: Listing 16.2.4.3.1.1, Listing 16.2.4.3.1.2
Source: Table 14.1.3.2.1.1

Table 40: Baseline Disease Characteristics – FAS (continued)

Characteristic		SYD985 N=291	Physician's Choice Total N=146	Lapatinib + Capecitabine N=27	Trastuzumab + Capecitabine N=24	Trastuzumab + Vinorelbine N=47	Trastuzumab + Eribulin N=46	Total N=437
Stage at Signing ICF, n (%)	IA	0	0	0	0	0	0	0
	IB	1 (0.3)	0	0	0	0	0	1 (0.2)
	IC	0	0	0	0	0	0	0
	II	2 (0.7)	2 (1.4)	1 (3.7)	0	0	1 (2.2)	4 (0.9)
	IIA	2 (0.7)	1 (0.7)	0	0	1 (2.1)	0	3 (0.7)
	IIB	3 (1.0)	3 (2.1)	1 (3.7)	0	1 (2.1)	1 (2.2)	6 (1.4)
	IIC	0	0	0	0	0	0	0
	III	11 (3.8)	5 (3.4)	3 (11.1)	0	1 (2.1)	1 (2.2)	16 (3.7)
	IIIA	2 (0.7)	1 (0.7)	0	0	1 (2.1)	0	3 (0.7)
	IIIB	1 (0.3)	1 (0.7)	0	0	1 (2.1)	0	2 (0.5)
	IIIC	4 (1.4)	5 (3.4)	2 (7.4)	2 (8.3)	1 (2.1)	0	9 (2.1)
	IV	217 (74.6)	105 (71.9)	16 (59.3)	17 (70.8)	34 (72.3)	36 (78.3)	322 (73.7)
	IVA	10 (3.4)	1 (0.7)	0	0	0	1 (2.2)	11 (2.5)
	IVB	4 (1.4)	0	0	0	0	0	4 (0.9)
	IVC	15 (5.2)	10 (6.8)	1 (3.7)	2 (8.3)	4 (8.5)	3 (6.5)	25 (5.7)
	Unknown	19 (6.5)	12 (8.2)	3 (11.1)	3 (12.5)	3 (6.4)	3 (6.5)	31 (7.1)

[1] Calculated in years as informed consent date - diagnosis date + 1/365.25.
[2] Calculated in years as informed consent date - diagnosis date of locally advanced or metastatic disease + 1/365.25.
[3] 'Unknown' also includes patients with HR status not available.
N/A = Not Applicable.
Listing Source: 16.2.4.3.1.1, 16.2.4.3.1.2
Program Name: t-14-01-03-02-01-01.sas, Date: 27JUL2021 9:10, Data cut-off 31MAR2021

Table 28: Central HER2 Assessment (FAS)

Characteristic, n (%)	SYD985 N=291	Physician's Choice N=146	Total N=437
Type of Tissue Used			
Archival	278 (95.5)	140 (95.9)	418 (95.7)
Fresh	13 (4.5)	6 (4.1)	19 (4.3)
Site of Collection			
Bone	6 (2.1)	5 (3.4)	11 (2.5)
Brain	5 (1.7)	5 (3.4)	10 (2.3)
Breast	167 (57.4)	81 (55.5)	248 (56.8)
Hepatic Lobe	19 (6.5)	12 (8.2)	31 (7.1)
Lung	21 (7.2)	12 (8.2)	33 (7.6)
Lymph Node	27 (9.3)	13 (8.9)	40 (9.2)
Skin	13 (4.5)	8 (5.5)	21 (4.8)
Other	33 (11.3)	10 (6.8)	43 (9.8)
Type			
Primary	159 (54.6)	78 (53.4)	237 (54.2)
Metastasis	132 (45.4)	68 (46.6)	200 (45.8)
HER2 IHC			
0	4 (1.4)	1 (0.7)	5 (1.1)
1+	0	0	0
2+	68 (23.4)	38 (26.0)	106 (24.3)
3+	216 (74.2)	105 (71.9)	321 (73.5)
Not Evaluable	1 (0.3)	1 (0.7)	2 (0.5)
Not Done	2 (0.7)	1 (0.7)	3 (0.7)

HER2 ISH							
Positive	261 (89.7)	133 (91.1)					394 (90.2)
Negative	1 (0.3)	0					1 (0.2)
Equivocal	0	1 (0.7)					1 (0.2)
Not Evaluable	7 (2.4)	3 (2.1)					10 (2.3)
Not Done	22 (7.6)	9 (6.2)					31 (7.1)
HER2 Status							
Positive	291 (100)	145 (99.3)					436 (99.8)
Negative	0	0					0

Table 29: Prior Systemic Therapy (Related to Study Indication)

Therapeutic Main Group (ATC Level 2) Preferred Name, n (%)	SYD985 N=291	Physician's Choice Total N=146	Lapatinib + Capecitabine N=27	Trastuzumab + Capecitabine N=24	Trastuzumab + Vinorelbine N=47	Trastuzumab + Eribulin N=46	Total N=437
No. Prior Treatment Regimens							
1-2	27 (9.3)	17 (11.6)	4 (14.8)	4 (16.7)	5 (10.6)	3 (6.5)	44 (10.1)
3-4	115 (39.5)	45 (30.8)	11 (40.7)	7 (29.2)	18 (38.3)	9 (19.6)	160 (36.6)
5-8	118 (40.5)	68 (46.6)	9 (33.3)	9 (37.5)	22 (46.8)	27 (58.7)	186 (42.6)
>8	31 (10.7)	16 (11.0)	3 (11.1)	4 (16.7)	2 (4.3)	7 (15.2)	47 (10.8)
Mean	6.3	6.5	6.7	7.1	5.8	6.9	6.4
Std. Dev.	3.13	3.29	4.14	3.75	2.52	3.05	3.19
Median	6.0	6.0	6.0	7.0	5.0	6.0	6.0
Min/Max	1/ 17	1/ 19	2/ 19	1/ 14	2/ 12	1/ 15	1/ 19
No. Prior Treatment Regimens in Metastatic Setting							
1-2	72 (24.7)	42 (28.8)	13 (48.1)	6 (25.0)	15 (31.9)	7 (15.2)	114 (26.1)
3	72 (24.7)	31 (21.2)	4 (14.8)	4 (16.7)	12 (25.5)	11 (23.9)	103 (23.6)
>=4	134 (46.0)	69 (47.3)	10 (37.0)	11 (45.8)	19 (40.4)	28 (60.9)	203 (46.5)
Mean	4.9	5.2	5.1	6.0	4.4	5.6	5.0
Std. Dev.	2.85	3.02	3.38	3.18	2.51	3.01	2.91
Median	4.0	5.0	4.0	6.0	4.0	5.0	4.0
Min/Max	1/ 16	1/ 14	1/ 14	2/ 12	1/ 11	1/ 13	1/ 16
No. HER2 Targeting Prior Treatment Regimens in Metastatic Setting							
1-2	102 (35.1)	56 (38.4)	17 (63.0)	9 (37.5)	19 (40.4)	10 (21.7)	158 (36.2)
>=3	174 (59.8)	83 (56.8)	9 (33.3)	11 (45.8)	27 (57.4)	35 (76.1)	257 (58.8)
Mean	4.0	4.0	3.8	4.4	3.5	4.5	4.0
Std. Dev.	2.29	2.22	2.20	2.23	2.06	2.27	2.26
Median	3.0	3.0	3.0	4.0	3.0	4.0	3.0
Min/Max	1/ 12	1/ 11	1/ 8	2/ 9	1/ 10	1/ 11	1/ 12
Prior Treatment Regimens [1]							
Trastuzumab + Pertuzumab + Taxane [2]	109 (37.5)	47 (32.2)	9 (33.3)	5 (20.8)	14 (29.8)	17 (37.0)	156 (35.7)
Trastuzumab + Pertuzumab	17 (5.8)	7 (4.8)	2 (7.4)	1 (4.2)	3 (6.4)	1 (2.2)	24 (5.5)
Trastuzumab + Capecitabine	31 (10.7)	19 (13.0)	2 (7.4)	1 (4.2)	5 (10.6)	10 (21.7)	50 (11.4)
Trastuzumab + Lapatinib	13 (4.5)	7 (4.8)	1 (3.7)	0	2 (4.3)	4 (8.7)	20 (4.6)
Trastuzumab + Vinorelbin	41 (14.1)	12 (8.2)	0	1 (4.2)	2 (4.3)	9 (19.6)	53 (12.1)
Trastuzumab + Eribulin	13 (4.5)	10 (6.8)	3 (11.1)	2 (8.3)	5 (10.6)	0	23 (5.3)
Trastuzumab-Emtansine	231 (79.4)	122 (83.6)	25 (92.6)	19 (79.2)	39 (83.0)	38 (82.6)	353 (80.8)
Lapatinib + Capecitabine	62 (21.3)	25 (17.1)	0	3 (12.5)	11 (23.4)	11 (23.9)	87 (19.9)
Other	225 (77.3)	110 (75.3)	19 (70.4)	21 (87.5)	34 (72.3)	35 (76.1)	335 (76.7)
Last Treatment Regimen before Study [1]							
Trastuzumab + Pertuzumab + Taxane [2]	2 (0.7)	4 (2.7)	0	0	0	3 (6.5)	6 (1.4)
Trastuzumab + Pertuzumab	3 (1.0)	1 (0.7)	0	0	1 (2.1)	0	4 (0.9)
Trastuzumab + Capecitabine	14 (4.8)	7 (4.8)	1 (3.7)	0	4 (8.5)	2 (4.3)	21 (4.8)
Trastuzumab + Lapatinib	2 (0.7)	3 (2.1)	0	0	2 (4.3)	1 (2.2)	5 (1.1)
Trastuzumab + Vinorelbin	14 (4.8)	3 (2.1)	0	0	0	3 (6.5)	17 (3.9)
Trastuzumab + Eribulin	6 (2.1)	5 (3.4)	1 (3.7)	1 (4.2)	3 (6.4)	0	11 (2.5)
Trastuzumab-Emtansine	84 (28.9)	44 (30.1)	14 (51.9)	10 (41.7)	11 (23.4)	9 (19.6)	128 (29.3)
Lapatinib + Capecitabine	19 (6.5)	9 (6.2)	0	0	6 (12.8)	3 (6.5)	28 (6.4)
Other	134 (46.0)	66 (45.2)	11 (40.7)	10 (41.7)	19 (40.4)	25 (54.3)	200 (45.8)
Antineoplastic Agents [1]	278 (95.5)	142 (97.3)	27 (100)	21 (87.5)	46 (97.9)	46 (100)	420 (96.1)
Trastuzumab	260 (89.3)	126 (86.3)	23 (85.2)	20 (83.3)	40 (85.1)	41 (89.1)	386 (88.3)
Trastuzumab Emtansine	255 (87.6)	128 (87.7)	26 (96.3)	19 (79.2)	42 (89.4)	40 (87.0)	383 (87.6)
Pertuzumab	177 (60.8)	84 (57.5)	19 (70.4)	14 (58.3)	27 (57.4)	22 (47.8)	261 (59.7)
Capecitabine	145 (49.8)	79 (54.1)	7 (25.9)	5 (20.8)	30 (63.8)	36 (78.3)	224 (51.3)
Docetaxel	123 (42.3)	57 (39.0)	10 (37.0)	9 (37.5)	21 (44.7)	16 (34.8)	180 (41.2)
Paclitaxel	103 (35.4)	64 (43.8)	11 (40.7)	14 (58.3)	17 (36.2)	21 (45.7)	167 (38.2)
Lapatinib	87 (29.9)	36 (24.7)	2 (7.4)	4 (16.7)	16 (34.0)	14 (30.4)	123 (28.1)
Vinorelbine	63 (21.6)	22 (15.1)	6 (22.2)	3 (12.5)	2 (4.3)	11 (23.9)	85 (19.5)
Vinorelbine Tartrate	34 (11.7)	15 (10.3)	2 (7.4)	3 (12.5)	0	10 (21.7)	49 (11.2)
Eribulin	31 (10.7)	18 (12.3)	8 (29.6)	3 (12.5)	7 (14.9)	0	49 (11.2)

Antineoplastic Agents [1] (cont.)							
Carboplatin	27 (9.3)	15 (10.3)	4 (14.8)	3 (12.5)	4 (8.5)	4 (8.7)	42 (9.6)
Cyclophosphamide	20 (6.9)	19 (13.0)	4 (14.8)	5 (20.8)	4 (8.5)	6 (13.0)	39 (8.9)
Investigational Antineoplastic Drugs	18 (6.2)	12 (8.2)	0	0	4 (8.5)	8 (17.4)	30 (6.9)
Neratinib	16 (5.5)	2 (1.4)	0	1 (4.2)	1 (2.1)	0	18 (4.1)
Lapatinib Ditosylate Monohydrate	15 (5.2)	8 (5.5)	0	1 (4.2)	3 (6.4)	4 (8.7)	23 (5.3)
Gemcitabine	14 (4.8)	7 (4.8)	1 (3.7)	0	2 (4.3)	4 (8.7)	21 (4.8)
Paclitaxel Albumin	14 (4.8)	6 (4.1)	2 (7.4)	0	3 (6.4)	1 (2.2)	20 (4.6)
Epirubicin	9 (3.1)	9 (6.2)	2 (7.4)	3 (12.5)	2 (4.3)	2 (4.3)	18 (4.1)
Palbociclib	8 (2.7)	6 (4.1)	1 (3.7)	2 (8.3)	1 (2.1)	2 (4.3)	14 (3.2)
Fluorouracil	7 (2.4)	10 (6.8)	1 (3.7)	3 (12.5)	1 (2.1)	5 (10.9)	17 (3.9)
Cyclophosphamide;epirubicin Hydrochloride;fluorouracil	6 (2.1)	2 (1.4)	1 (3.7)	0	0	1 (2.2)	8 (1.8)
Gemcitabine Hydrochloride	6 (2.1)	5 (3.4)	2 (7.4)	2 (8.3)	0	1 (2.2)	11 (2.5)
Margetuximab	6 (2.1)	0	0	0	0	0	6 (1.4)
Eribulin Mesilate	5 (1.7)	3 (2.1)	1 (3.7)	0	0	1 (2.2)	8 (1.8)
Pegylated Liposomal Doxorubicin Hydrochloride	5 (1.7)	3 (2.1)	1 (3.7)	0	2 (4.3)	0	8 (1.8)
Abemaciclib	4 (1.4)	1 (0.7)	0	0	1 (2.1)	0	5 (1.1)
Doxorubicin	4 (1.4)	9 (6.2)	2 (7.4)	4 (16.7)	0	3 (6.5)	13 (3.0)
Bevacizumab	3 (1.0)	3 (2.1)	1 (3.7)	0	0	2 (4.3)	6 (1.4)
Liposomal Doxorubicin Hydrochloride	3 (1.0)	1 (0.7)	0	0	0	1 (2.2)	4 (0.9)

Antineoplastic Agents [1] (cont.)							
Poziotinib	3 (1.0)	0	0	0	0	0	3 (0.7)
Cisplatin	2 (0.7)	2 (1.4)	0	0	1 (2.1)	1 (2.2)	4 (0.9)
Everolimus	2 (0.7)	2 (1.4)	0	1 (4.2)	0	1 (2.2)	4 (0.9)
Pembrolizumab	2 (0.7)	0	0	0	0	0	2 (0.5)
Tucatinib	2 (0.7)	2 (1.4)	0	0	0	2 (4.3)	4 (0.9)
Afatinib	1 (0.3)	1 (0.7)	0	1 (4.2)	0	0	2 (0.5)
Alpelisib	1 (0.3)	0	0	0	0	0	1 (0.2)
Combinations Of Antineoplastic Agents	1 (0.3)	0	0	0	0	0	1 (0.2)
Cyclophosphamide;fluorouracil;methotrexate	1 (0.3)	1 (0.7)	0	0	0	1 (2.2)	2 (0.5)
Doxorubicin Hydrochloride	1 (0.3)	0	0	0	0	0	1 (0.2)
Etoposide	1 (0.3)	1 (0.7)	0	0	0	1 (2.2)	2 (0.5)
Gemcitabine;paclitaxel	1 (0.3)	0	0	0	0	0	1 (0.2)
Ibrutinib	1 (0.3)	0	0	0	0	0	1 (0.2)
Mcla 128	1 (0.3)	0	0	0	0	0	1 (0.2)
Methotrexate Sodium	1 (0.3)	0	0	0	0	0	1 (0.2)
Pegylated Liposomal Doxorubicin	1 (0.3)	1 (0.7)	0	1 (4.2)	0	0	2 (0.5)
Ribociclib	1 (0.3)	0	0	0	0	0	1 (0.2)
Tas 116	1 (0.3)	1 (0.7)	0	1 (4.2)	0	0	2 (0.5)
Taselisib	1 (0.3)	0	0	0	0	0	1 (0.2)
Temsirolimus	1 (0.3)	0	0	0	0	0	1 (0.2)

Antineoplastic Agents [1] (cont.)							
Atezolizumab	0	1 (0.7)	0	0	0	1 (2.2)	1 (0.2)
Buparlisib	0	1 (0.7)	0	1 (4.2)	0	0	1 (0.2)
Cyclophosphamide;doxorubicin	0	1 (0.7)	0	0	0	1 (2.2)	1 (0.2)
Epirubicin Hydrochloride	0	1 (0.7)	1 (3.7)	0	0	0	1 (0.2)
Ixabepilone	0	1 (0.7)	1 (3.7)	0	0	0	1 (0.2)
Lurbinectedin	0	1 (0.7)	0	0	0	1 (2.2)	1 (0.2)
Methotrexate	0	1 (0.7)	0	0	1 (2.1)	0	1 (0.2)
Mitomycin	0	2 (1.4)	1 (3.7)	0	0	1 (2.2)	2 (0.5)
Mitoxantrone	0	2 (1.4)	1 (3.7)	0	0	1 (2.2)	2 (0.5)
Monoclonal Antibodies	0	1 (0.7)	1 (3.7)	0	0	0	1 (0.2)
Taxanes	0	1 (0.7)	0	0	0	1 (2.2)	1 (0.2)
Varlitinib	0	1 (0.7)	1 (3.7)	0	0	0	1 (0.2)
Endocrine Therapy [1]	110 (37.8)	56 (38.4)	8 (29.6)	12 (50.0)	19 (40.4)	17 (37.0)	166 (38.0)
Letrozole	61 (21.0)	34 (23.3)	4 (14.8)	8 (33.3)	11 (23.4)	11 (23.9)	95 (21.7)
Exemestane	38 (13.1)	16 (11.0)	2 (7.4)	2 (8.3)	7 (14.9)	5 (10.9)	54 (12.4)
Fulvestrant	33 (11.3)	15 (10.3)	3 (11.1)	2 (8.3)	6 (12.8)	4 (8.7)	48 (11.0)
Tamoxifen	31 (10.7)	17 (11.6)	2 (7.4)	4 (16.7)	3 (6.4)	8 (17.4)	48 (11.0)
Anastrozole	17 (5.8)	7 (4.8)	2 (7.4)	2 (8.3)	2 (4.3)	1 (2.2)	24 (5.5)
Goserelin	6 (2.1)	5 (3.4)	2 (7.4)	0	1 (2.1)	2 (4.3)	11 (2.5)
Tamoxifen Citrate	5 (1.7)	3 (2.1)	0	1 (4.2)	1 (2.1)	1 (2.2)	8 (1.8)
Leuprorelin Acetate	2 (0.7)	0	0	0	0	0	2 (0.5)
Aromatase Inhibitors	1 (0.3)	0	0	0	0	0	1 (0.2)

Endocrine Therapy [1] (cont.)							
Enzalutamide	1 (0.3)	0	0	0	0	0	1 (0.2)
Leuprorelin	1 (0.3)	0	0	0	0	0	1 (0.2)
Megestrol Acetate	1 (0.3)	2 (1.4)	1 (3.7)	0	1 (2.1)	0	3 (0.7)
Abiraterone Acetate	0	1 (0.7)	0	1 (4.2)	0	0	1 (0.2)

[1] Only medications in the metastatic setting are presented.
[2] Taxane can include paclitaxel and docetaxel.
Note: Medications are coded by using WHO Drug Global B3, SEP2020.
Note: Patients are counted once per therapeutic main group and preferred name.
Listing Source: 16.2.4.5.1
Program Name: t-14-01-04-01-01.sas, Date: 18AUG2021 4:51, Data cut-off 31MAR2021

Numbers analysed

The applicant presents data from 437 HER2+ breast cancer patients from the pivotal study SYD985.002..

Outcomes and estimation

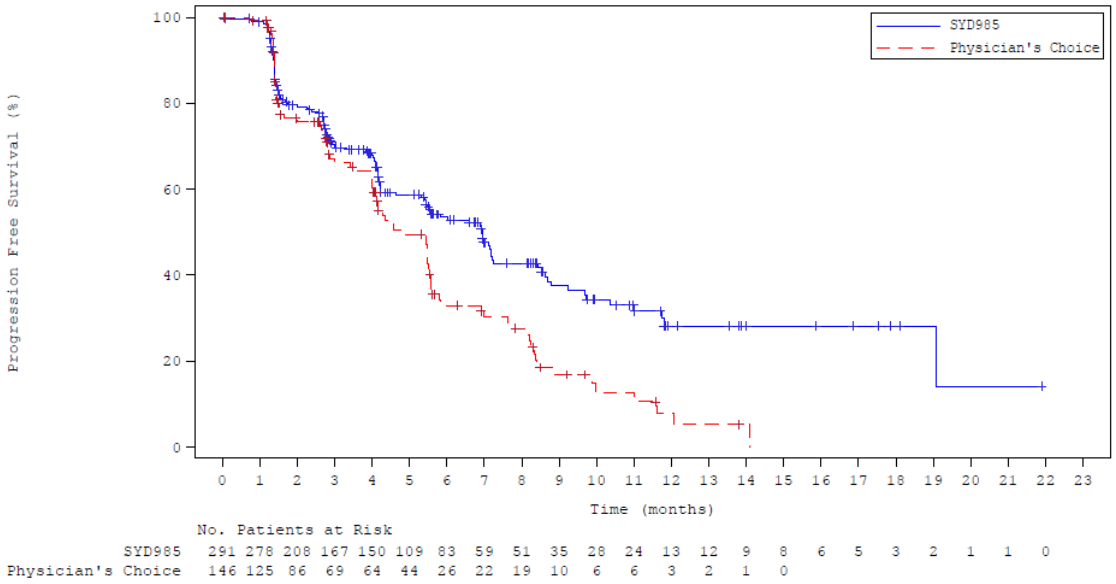
Primary endpoint – PFS by IRC (DCO: 31Mar2021)

Table 30: Progression-Free Survival – Independent Central Review. Primary Analysis – FAS

PFS	SYD985 N=291	Physician's Choice N=146
Progressed (event), n (%)	138 (47.4)	86 (58.9)
Died (event), n (%)	2 (0.7)	0
Censored, n (%)	151 (51.9)	60 (41.1)
Kaplan-Meier estimate of PFS (months)		
1st quartile (95% CI)	2.7 (1.7, 3.0)	2.6 (1.4, 2.9)
Median (95% CI)	7.0 (5.4, 7.2)	4.9 (4.0, 5.5)
3rd quartile (95% CI)	19.1 (11.0, NE)	8.2 (5.8, 9.9)
p-value [1]	0.002	
Hazard ratio (95% CI) [2]	0.6401 (0.4885, 0.8389)	

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[1] P-value from stratified log-rank test for median estimate of PFS: stratified according to the randomization stratification factors.
[2] Hazard ratio calculated using the Cox proportional hazards model, stratified similarly to the log-rank test.
Note: PFS was defined as the time (in months) from the date of randomization to the date of first documented disease progression (independent central review assessed) according to RECIST v1.1 or death due to any cause (whichever occurred earlier).
Cross-reference: Listing 16.2.1.1, Listing 16.2.6.1
Source: Table 14.2.1.1.1

Figure 10: Kaplan-Meier Plot of Progression-Free Survival – Independent Central Review. Primary Analysis – FAS



Abbreviations: FAS, full analysis set; RECIST, Response Evaluation Criteria in Solid Tumors.
Note: Progression-free survival was defined as the time (in months) from the date of randomization to the date of first documented disease progression (independent central review assessed) according to RECIST v1.1 or death due to any cause (whichever occurred earlier).
Cross-reference: Listing 16.2.1.1, Listing 16.2.6.1
Source: Figure 14.2.1.1.2

Sensitivity analyses

Table 31: Progression-Free Survival – Sensitivity Analyses – FAS

PFS	N	Progressed (event) n (%)	Died (event) n (%)	Median PFS (95% CI)	Hazard Ratio (95% CI) p-value
Primary analysis [1]					
SYD985	291	138 (47.4)	2 (0.7)	7.0 (5.4, 7.2)	0.6401 (0.4885, 0.8389)
Physician's choice	146	86 (58.9)	0	4.9 (4.0, 5.5)	0.002 [3]
Actual treatment and strata [1]					
SYD985	288	138 (47.9)	2 (0.7)	7.0 (5.5, 7.2)	0.5950 (0.4521, 0.7832)
Physician's choice	137	86 (62.8)	0	4.9 (4.0, 5.5)	<0.001 [3]
Without any stratification factors [1]					
SYD985	291	138 (47.4)	2 (0.7)	7.0 (5.4, 7.2)	0.6361 (0.4857, 0.8331)
Physician's choice	146	86 (58.9)	0	4.9 (4.0, 5.5)	0.001 [4]
Earliest calculated progression date from independent central or local review [1]					
SYD985	291	173 (59.5)	2 (0.7)	5.5 (4.2, 6.8)	0.6230 (0.4900, 0.7922)
Physician's choice	146	110 (75.3)	0	4.1 (3.4, 4.6)	<0.001 [3]
Worst case (progression date one day after the last tumor evaluation where progression was not known to have occurred [2]					
SYD985	291	138 (47.4)	2 (0.7)	5.8 (4.6, 7.8)	0.6080 (0.4638, 0.7972)
Physician's choice	146	86 (58.9)	0	4.1 (2.8, 4.2)	<0.001 [3]

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[1] PFS was defined as the time (in months) from the date of randomization to the date of first documented disease progression (independent central review assessed) according to RECIST v1.1 or death due to any cause (whichever occurred earlier).
[2] PFS was defined as the time (in months) from the date of randomization to the date of the worst-case documented disease progression (independent central review assessed) according to RECIST v1.1 or death due to any cause (whichever occurred earlier).
[3] Hazard ratio calculated using the Cox proportional hazards model, stratified similarly to the log-rank test. P-value from stratified log-rank test for median estimate of PFS: stratified according to the randomization stratification factors.
[4] Hazard ratio calculated using the Cox proportional hazards model. P-value from log-rank test for median estimate of PFS.
Cross-reference: Listing 16.2.1.1, Listing 16.2.6.1
Source: Table 14.2.1.1.1, Table 14.2.1.3.1, Table 14.2.1.4.1, Table 14.2.1.5.1, Table 14.2.1.6.1

Event or censoring description by treatment

Table 32: Time to PFS ICR - Frequencies

Table of Event or Censoring Description by Treatment			
	Treatment		
Event or Censoring Description	Physician Choice	SYD985	Total
Death Between Adequate Assessment Visits	0 0.00	1 0.34	1
Death before 1st PD Assessment	0 0.00	1 0.34	1
No Baseline Tumour Assessments	3 2.05	3 1.03	6
No Post-Baseline Tumour Assessments	16 10.96	5 1.72	21
No Progression. Ongoing	1 0.68	5 1.72	6
Progression between Scheduled Visits	86 58.90	138 47.42	224
Trt. Disc. for Toxicity or Other Reason	12 8.22	92 31.62	104
Trt. Disc. for Undocumented Prog	28 19.18	46 15.81	74
Total	146	291	437

Secondary Endpoints

<u>Overall Survival</u> (DCO 30 June 2022)

An update of the overall survival analysis with an additional 15 months follow-up (June 30, 2022) compared to the previous one (March 31, 2021) has been provided (final OS data).

Table 33: Final Overall Survival – FAS (OS database lock, cut-off 30 June 2022)

OS	SYD985 N=291	Physician's Choice N=146
Died (Event), n (%)	181 (62.2)	94 (64.4)
Censored, n (%)	110 (37.8)	52 (35.6)
Kaplan Meier Estimate of OS (Months)		
1st Quartile (95% CI)	10.1 (8.5, 11.9)	10.8 (8.9, 12.0)
Median (95% CI)	21.0 (18.1, 25.0)	19.5 (14.2, 23.1)
3rd Quartile (95% CI)	NE (39.4, NE)	NE (30.7, NE)
1 Year Survival Estimate (%) (95% CI)	69.8 (64.1, 74.9)	68.0 (59.5, 75.1)
p-value [1]	0.236	
Hazard ratio (95% CI) [2]	0.8680 (0.6760, 1.1145)	

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; NE, not estimable; OS, overall survival.
[1] P-value from stratified log-rank test for Kaplan Meier estimate of median OS: stratified according to the randomization stratification factors.
[2] Hazard ratio calculated using Cox's proportional hazards model, stratified similarly to the log-rank test.
Note: OS is defined as the time (in months) from date of randomization to date of death due to any cause. If the patient does not have a documented date of death, OS will be censored at the date of the patient was last known to be alive.

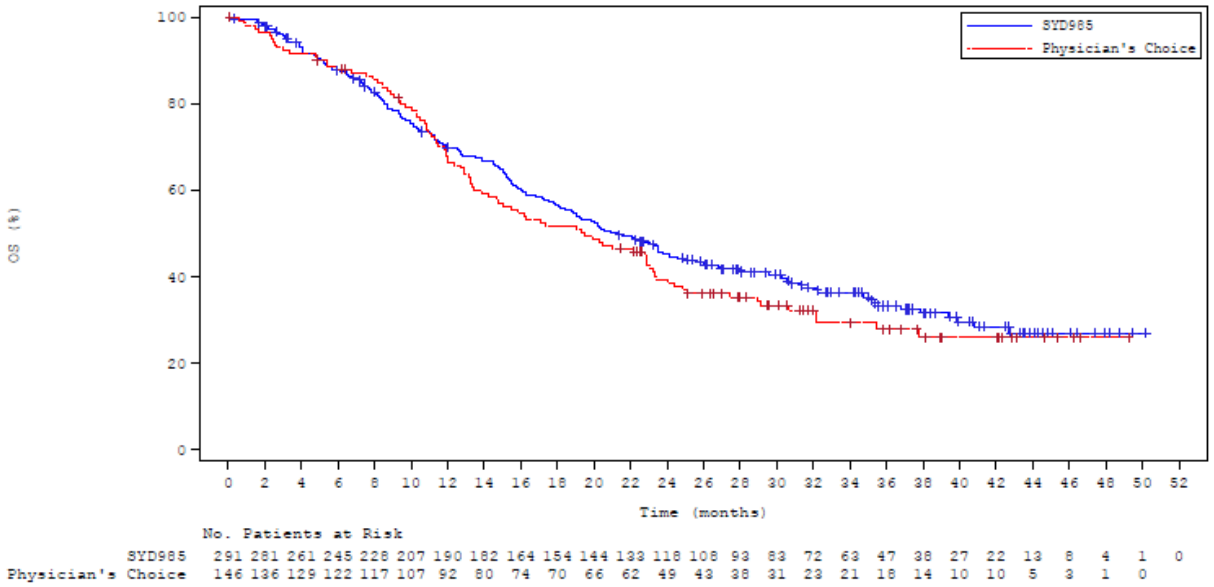


Figure 20: Kaplan-Meier Plot of Overall Survival in Months – FAS (OS database lock, cut-off 30 June 2022)
Abbreviations: FAS, full analysis set; OS, overall survival. Note: OS was defined as the time (in months) from the date of randomization to the date of death due to any cause.

***Objective Response Rate* (DCO: 30 March 2021)**

ORR was defined as the percentage of patients with ICR-assessed best overall response of CR or PR according to RECIST v1.1 (i.e., "responders").

Table 34: Objective Response Rate – FAS

ORR [1], n (%)	SYD985 N=291	Physician's Choice N=146
Measurable disease at baseline	252 (86.6)	122 (83.6)
Responder	70 (27.8)	36 (29.5)
95% CIs [2]	22.3, 33.7	21.6, 38.4
Non-responder	182 (72.2)	86 (70.5)
p-value [3]	0.732	

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.
Note: The denominator is all patients in the FAS with measurable disease at baseline.
[1] ORR was defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 (ie, "responders"). Only patients with measurable disease at baseline were included in the analysis of ORR. Patients without a postbaseline tumor assessment were considered non-responders.
[2] The 95% CIs were computed using the exact binomial method.
[3] P-value from Cochran-Mantel-Haenszel test including the randomization stratification factors.
Cross-reference: Listing 16.2.1.1, Listing 16.2.6.3.1
Source: Table 14.2.2.2.1

Table 35: Best overall tumour response, FAS

		SYD985 (N=291)	Physician's choice (N=146)
ICR	Measurable disease at baseline, n (%)	252 (86.6)	122 (83.6)
	CR, n (%)	5 (2.0)	1 (0.8)
	PR, n (%)	65 (25.8)	35 (28.7)
	Confirmed CR, n (%)	5 (2.0)	1 (0.8)
	Confirmed PR, n (%)	46 (18.3)	25 (20.5)
Investigator assessed	Measurable disease at baseline, n (%)	264 (90.7)	130 (89.0)
	CR, n (%)	6 (2.3)	2 (1.5)
	PR, n (%)	67 (25.4)	29 (22.3)
	Confirmed CR, n (%)	6 (2.3)	1 (0.8)
	Confirmed PR, n (%)	50 (18.9)	24 (18.5)

***Patient-Reported Outcomes* (DCO: 30 March 2021)**

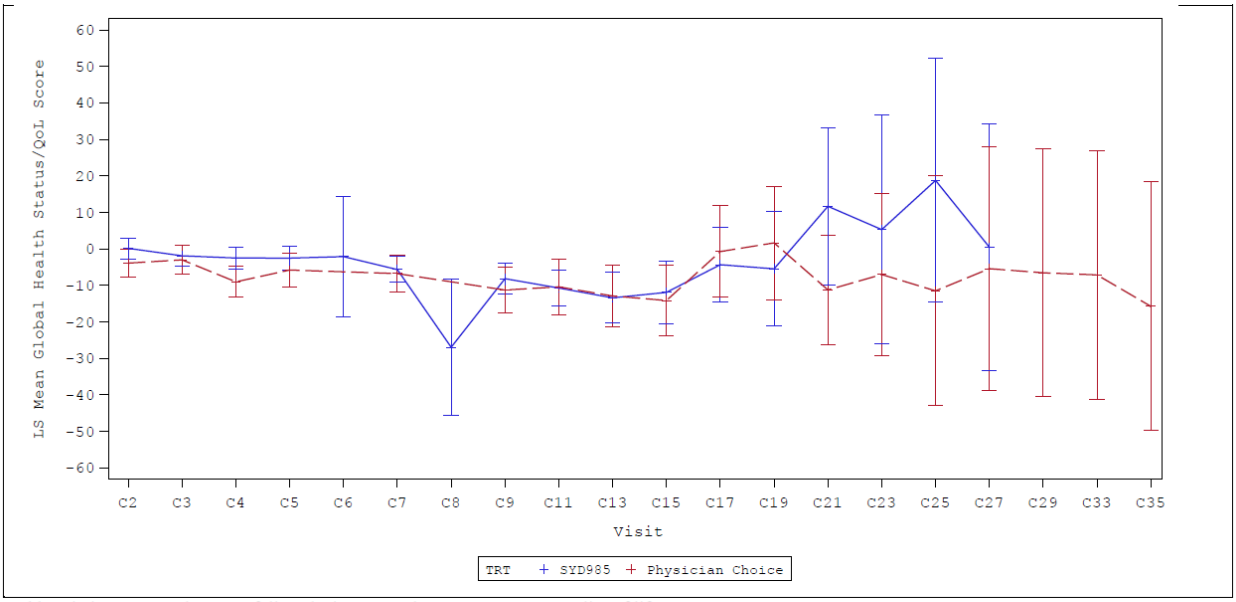
PROs for health-related QoL were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23.

Table 36: EORTC QLQ-C30 Quality of Life transformed scores – FAS

	SYD985		Physician's choice	
	Baseline	End of treatment	Baseline	End of treatment
Overall mean global health status				
N	253	132	123	66
Mean (SD)	64.5 (23.1)	54.3 (21.7)	62.4 (22.1)	54.8 (22.7)
Overall mean physical functioning score				
N	254	134	123	66
Mean (SD)	79.2 (22.0)	72.8 (22.5)	76.9 (19.9)	69.8 (24.1)
Overall mean role functioning score				
N	254	134	123	66
Mean (SD)	76.8 (29.4)	65.3 (28.8)	75.2 (26.4)	66.7 (31.1)
Overall mean emotional functioning score				
N	253	134	123	66
Mean (SD)	71.5 (22.4)	68.6 (23.6)	72.2 (18.9)	65.8 (24.6)
Overall mean cognitive functioning score				
N	252	134	123	66
Mean (SD)	83.9 (20.2)	78.1 (24.6)	85.6 (16.7)	77.8 (22.1)
Overall mean social functioning score				
N	253	134	123	66
Mean (SD)	76.7 (27.6)	70.5 (28.0)	77.2 (23.3)	69.2 (30.8)

Note: A high score for the global health status and a functional scale represents a high level of functioning.

Figure 11: Linear Plot of Least Squared Means of Change From Baseline of Global Health Status/Quality of Life Transformed Score – FAS



Abbreviations: C, Cycle; FAS, full analysis set; LS, least square; QoL, quality of life; TRT, treatment.
Error bars represent 95% CI for the LS means.
Note: QoL scale score, 0 to 100, and a high scale score represent a higher response level; analysis variable is difference in QoL scale (cycle minus baseline where baseline is the last available score before the first dose of study treatment).
Covariance structures tested: unstructured, variance components, compound symmetry, and first-order autoregressive. Covariance structure with lowest Akaike's information criterion (AIC) was used: first-order autoregressive
Cross-reference: Listing 16.2.6.5.1
Source: Figure 14.2.2.4.8.1.2

Exploratory Endpoints

Time to response (TTR) (DCO: 30 March 2021)

TTR was defined as the time between the date of randomisation until first documented response (CR or PR) according to RECIST v1.1.

About 25% of patients in the FAS had a documented response (CR or PR) at any point during the study as assessed by ICR (SYD985, 24.7%; physician's choice, 24.7%) and local review (SYD985, 25.8%; physician's choice, 21.2%). Because of the high number of censored patients in both treatment groups (>74% of patients in both treatment groups did not have a response), a median Kaplan-Meier estimate of TTR could not be determined in both treatment groups for response data assessed by ICR and in the physician's choice group for local review data. Therefore, interpretation of median TTR is not possible.

Table 50: Time to Response (TTR) – Independent Central and Local Review (FAS)

TTR	SYD985 N=291	Physician's Choice N=146
Independent Central Review		
Response (Event), n (%)	72 (24.7)	36 (24.7)
Censored, n (%)	219 (75.3)	110 (75.3)
Kaplan Meier Estimate of TTR (Months)		
1st Quartile (95% CI)	2.9 (2.8, 4.2)	2.8 (1.8, 4.1)
Median (95% CI)	NE (8.3, NE)	NE (5.4, NE)
3rd Quartile (95% CI)	NE (NE, NE)	NE (NE, NE)
Local Review		
Response (Event), n (%)	75 (25.8)	31 (21.2)
Censored, n (%)	216 (74.2)	115 (78.8)
Kaplan Meier Estimate of TTR (Months)		
1st Quartile (95% CI)	4.2 (2.8, 5.4)	4.2 (1.5, 5.6)
Median (95% CI)	13.9 (8.3, NE)	NE (NE, NE)
3rd Quartile (95% CI)	NE (13.9, NE)	NE (NE, NE)

Duration of response (DOR) (DCO: 30 March 2021)

DOR was defined as the time from the first documented tumour response (CR or PR) to the date of first documented disease progression or to death due to any cause, whichever occurred first.

Median DOR (Kaplan-Meier estimates) was 15.1 months in the SYD985 group and 4.6 months in the physician's choice group based on central review data. Results from local review were 6.9 months (SYD985) and 4.4 months (physician's choice). This analysis is based on a small subset of patients (about 25% or less of patients in the FAS) who first had documented tumour response and then progressed or died. Results are not robust and should be interpreted with caution. Updated results are expected to better characterise the response to treatment.

Table 371: Duration of Response (DOR) – Independent Central and Local Review (FAS)

DOR	SYD985 N=291	Physician's Choice N=146
Independent Central Review		
Responders, n (%)	70 (24.1)	36 (24.7)
Progressed (Event), n (%)	19 (27.1)	21 (58.3)
Died (Event), n (%)	1 (1.4)	0
Censored, n (%)	50 (71.4)	15 (41.7)
Kaplan Meier Estimate of DOR (Months)		
1st Quartile (95% CI)	4.2 (2.8, 5.9)	2.8 (1.5, 4.2)
Median (95% CI)	15.1 (5.7, 15.1)	4.6 (2.8, 7.1)
3rd Quartile (95% CI)	15.1 (NE, NE)	7.6 (5.6, NE)
Independent Local Review		
Responders, n (%)	73 (25.1)	31 (21.2)
Progressed (Event), n (%)	25 (34.2)	22 (71.0)
Died (Event), n (%)	3 (4.1)	0
Censored, n (%)	45 (61.6)	9 (29.0)
Kaplan Meier Estimate of DOR (Months)		
1st Quartile (95% CI)	4.2 (2.9, 5.1)	3.5 (1.4, 4.2)
Median (95% CI)	6.9 (4.5, NE)	4.4 (3.5, 6.6)
3rd Quartile (95% CI)	NE (11.1, NE)	7.5 (5.6, 12.7)

Clinical Benefit Rate (CBR) (DCO: 30 March 2021)

CBR was defined as the proportion of patients with CR, PR, or stable disease (stable disease for ≥6 months) for patients with measurable disease, or with CR or non-CR/non-PD (non-CR/non-PD for ≥6 months) for patients with non-measurable disease.

The CBR was higher in the SYD985 group than in the physician's choice group (ICR: SYD985, 38.5%; physician's choice, 32.2%; local review: SYD985, 35.4%; physician's choice, 28.8%).

Table 38: Clinical Benefit Rate Based on Best Overall Response – Independent Central and Local Review – FAS

CBR [1]	SYD985 N=291	Physician's Choice N=146
Independent central review		
Clinical benefit, n (%)	112 (38.5)	47 (32.2)
95% CIs [2]	32.9, 44.3	24.7, 40.4
No clinical benefit, n (%)	179 (61.5)	99 (67.8)
Local review		
Clinical benefit, n (%)	103 (35.4)	42 (28.8)
95% CIs [2]	29.9, 41.2	21.6, 36.8
No clinical benefit, n (%)	188 (64.6)	104 (71.2)

Abbreviations: CBR, clinical benefit rate; CR, complete response; FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[1] CBR was defined as the percentage of patients with a CR, PR, or stable disease (stable disease for 6 months or longer) for patients with measurable disease, or CR or non-CR/non-PD (non-CR/non-PD for 6 months or longer) for patients with non-measurable disease according to RECIST v1.1.
[2] The 95% CIs were computed using the exact binomial method.
Cross-reference: Listing 16.2.6.3.1, Listing 16.2.6.3.2
Source: Table 14.2.2.7

Table 39: Patients with measurable disease on baseline only (FAS)

		SYD985 (N=291)	Physician's choice (N=146)
ICR	Measurable disease at baseline, n (%)	252 (86.6%)	122 (83.6%)
	CR, n (%) (confirmed & unconfirmed)	5 (2.0%)	1 (0.8%)
	PR, n (%) (confirmed & unconfirmed)	65 (25.8%)	35 (28.7%)
	SD, n (%)	120 (47.6%)	45 (36.9%)
	PD, n (%)	57 (22.6%)	28 (23.0%)
	Not evaluable, n (%)	5 (2.0%)	13 (10.7%)
	Not Available, n (%)	0	0
Investigator assessed	Measurable disease at baseline, n (%)	264 (90.7%)	130 (89.0%)
	CR, n (%) (confirmed & unconfirmed)	6 (2.3%)	2 (1.5%)
	PR, n (%) (confirmed & unconfirmed)	67 (25.4%)	29 (22.3%)
	SD, n (%)	138 (52.3%)	66 (50.8%)
	PD, n (%)	48 (18.2%)	23 (17.7%)
	Not evaluable, n (%)	2 (0.8%)	0
	Not available*, n (%)	3 (1.1%)	10 (7.7%)

* No best response available since no in-treatment RECIST evaluations available

Table 40: Patients with measurable and non-measurable disease on baseline (FAS)

		SYD985 (N=291)	Physician's choice (N=146)
ICR	CR, n (%) (confirmed & unconfirmed)	7 (2.4%)	1 (0.7%)
	PR, n (%) (confirmed & unconfirmed)	65 (22.3%)	35 (24.0%)
	SD or Non-CR/non-PD, n(%)	148 (50.9%)	55 (37.7%)
	PD, n (%)	62 (21.3%)	32 (21.9%)
	Not evaluable, n (%)	8 (2.7%)	21 (14.4%)
	Not Available, n (%)	1 (0.3%)	2 (1.4%)
Investigator assessed	CR, n (%) (confirmed & unconfirmed)	7 (2.4%)	2 (1.4%)
	PR, n (%) (confirmed & unconfirmed)	68 (23.4%)	29 (19.9%)
	SD or Non-CR/non-PD, n(%)	157 (54.0%)	72 (49.3%)
	PD, n (%)	50 (17.2%)	24 (16.4%)
	Not evaluable, n (%)	2 (0.7%)	0
	Not Available*, n (%)	7 (2.4%)	19 (13.0%)

* No best response available since no in-treatment RECIST evaluations available

Reduction in target lesion (DCO: 30 March 2021)

Reduction in Target Lesion Measurement is not considered as a relevant endpoint to assess clinical benefit of SYD985 as a measurable reduction in target lesions does not necessarily translate into a tumour response according to RECIST v1.1. The number of patients with a tumour reduction as shown in Table 48 is different from the number of responders in Table 55 (Objective Response Rate – FAS).

Table 41: Reduction in Target Lesion Measurement – Independent Central and Local Review – FAS

Target Lesion Measurement	SYD985 N=291	Physician's Choice N=146
Independent central review		
Reduction, n (%)	177 (70.2)	71 (58.2)
95% CIs [1]	64.2, 75.8	48.9, 67.1
No reduction, n (%)	75 (29.8)	51 (41.8)
Local review		
Reduction, n (%)	185 (70.1)	79 (60.8)
95% CIs [1]	64.2, 75.5	51.8, 69.2
No reduction, n (%)	79 (29.9)	51 (39.2)

Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with data available.
Note: The denominator is all patients in the FAS with measurable disease at baseline.
[1] The 95% CIs were computed using the exact binomial method.
Cross-reference: Listing 16.2.6.3.1, Listing 16.2.6.3.2
Source: Table 14.2.2.8.1

Survival Follow-Up (DCO: 30 March 2021)

Mean and median time from last dose to tumour progression was longer under SYD985 treatment than under treatment according to physician's choice for patients who discontinued treatment for a non-PD reason (mean: SYD985, 187.8 days; physician's choice, 136.1 days; median: SYD985, 158.0 days; physician's choice, 114.0 days). For time from last dose to first subsequent anticancer therapy (for all patients in the FAS) or to second progression (only for patients who discontinued treatment due to disease progression), median times were comparable between SYD985 and TPC.

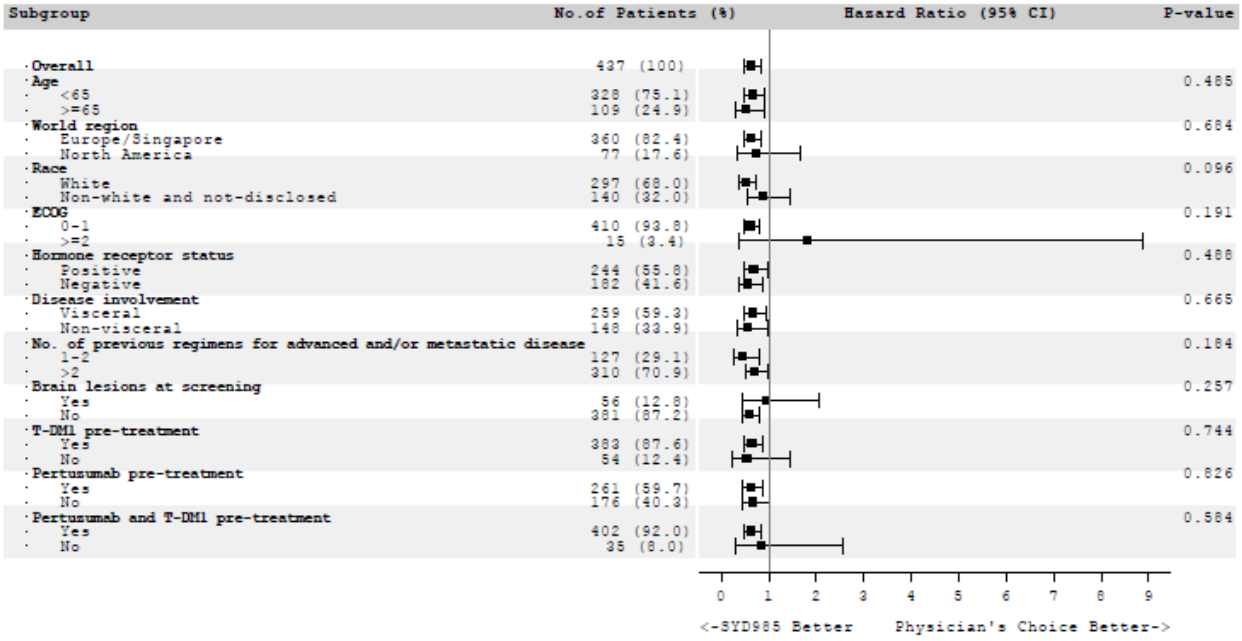
Table 42: Survival Follow up - FAS

Parameter (Days)	Statistic	SYD985 N=291	Physician's Choice N=146
Time to progression from last dose [1]	n	55	13
	Mean	187.8	136.1
	SD	135.53	55.65
	Median	158.0	114.0
	Min/max	40/810	72/262
Time to first subsequent anticancer therapy from last dose [2]	n	176	100
	Mean	183.5	169.5
	SD	178.46	174.73
	Median	106.0	111.0
	Min/max	15/925	2/890
Time to second progression from last dose [3]	n	60	58
	Mean	183.6	174.9
	SD	118.37	123.00
	Median	146.5	159.5
	Min/max	9/716	-1/667

Abbreviations: FAS, full analysis set; Max, maximum; Min, minimum; N, number of patients in treatment group; n, number of patients with data available.
[1] Time to progression (days) = progression date - last dose date + 1 (for patients who discontinued treatment for a non-progressive disease reason).
[2] Time to start first subsequent anticancer therapy (days) = first anticancer therapy date - last dose date + 1 (for all patients).
[3] Time to second progression (days) = progression date - last dose date + 1 (for patients who discontinued treatment due to disease progression).
Note: The minimum time of -1 day from last dose to second progression refers to Patient [redacted]
Cross-reference: Listing 16.2.6.11
Source: Table 14.2.2.1.4

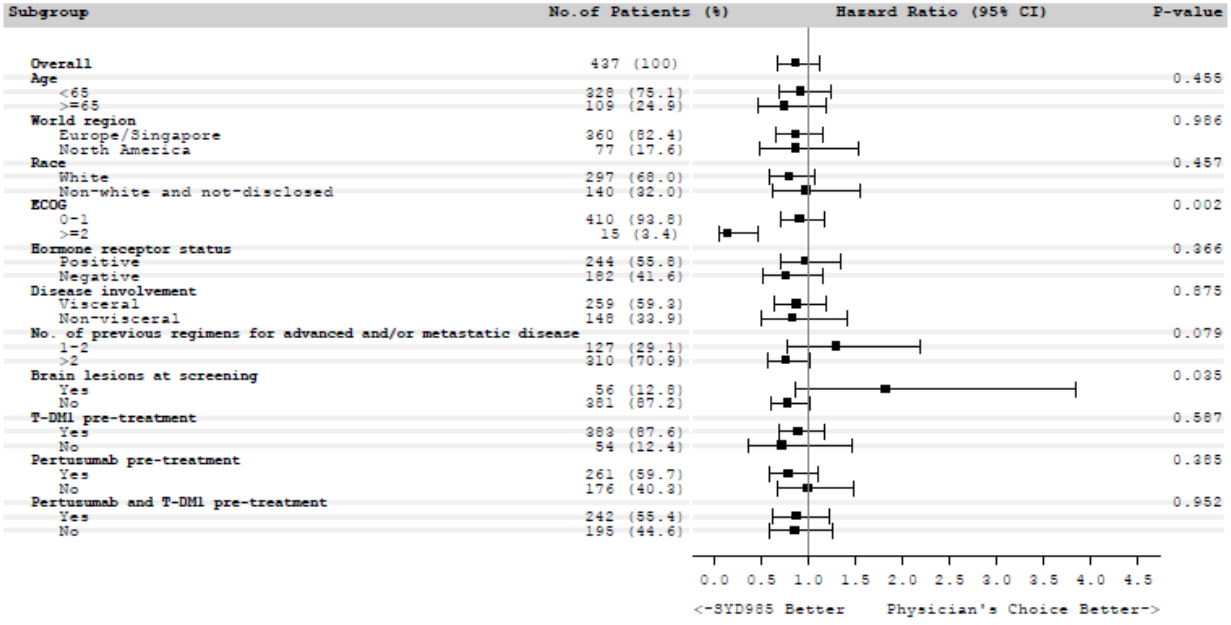
Ancillary analyses

Figure 22: Forest Plot of Progression-Free Survival – Independent Central Review. Sensitivity Analysis – FAS - DCO: 30 March 2021)



Abbreviations: ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; T-DM1, [ado-]trastuzumab emtansine.
Note: For "world region" and "number of previous regimens for advanced and/or metastatic disease," the planned values were used (ie, from stratification); for "pertuzumab pretreatment," the actual values were used and not the planned values from stratification.
Note: The ECOG subgroup ">=2" only included patients with ECOG=2 (Listing 16.2.8.2.6).
Cross-reference: Listing 16.2.1.1, Listing 16.2.4.1, Listing 16.2.4.3.1.1, Listing 16.2.4.3.1.2, Listing 16.2.4.4, Listing 16.2.6.1, Listing 16.2.8.2.6
Source: Figure 14.2.1.8

Figure 3: Forest Plot of Plot of Final Overall Survival (OS). Sensitivity Analysis (FAS) – DCO: 30 June 2022)



3.3.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 43: Summary of efficacy for trial SYD985.002

Title: A multi-centre, open-label, randomized clinical trial comparing the efficacy and safety of the antibody-drug conjugate SYD985 to physician's choice in patients with HER2-positive unresectable locally advanced or metastatic breast cancer			
Study identifier	SYD985.002 ; EudraCT Number: 2017-001994-18 ; IND Number: 131333		
Design	This study is designed as a randomised, active-controlled, superiority study in patients with unresectable locally advanced or metastatic HER2-positive breast cancer. The patients should have had either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-)trastuzumab emtansine treatment. Eligible patients will be randomly assigned (2:1) to receive SYD985 or physician's choice treatment until disease progression, unacceptable toxicity or study termination by the Sponsor. During treatment, patients will have to visit the clinical site to assess efficacy, quality of life (QoL), and safety using standardised criteria.		
	Duration of main phase		After a screening period of maximally 28 days, patients who are eligible will be randomised and treated until disease progression or unacceptable toxicity. Upon treatment discontinuation patients should return for a treatment discontinuation visit 4-6 weeks after the last administration of study drug. Thereafter patients will be contacted to follow up on clinical disease progression, unresolved AEs, new anticancer therapies, and overall survival every 3 months after the treatment discontinuation visit up to death, lost to follow-up, consent withdrawal or end of study data collection, whichever comes first.
Hypothesis	The primary objective of this study is: - To demonstrate that SYD985 is superior to physician's choice in prolonging progression-free survival (PFS) on the basis of the blinded independent central review of tumour assessment. The secondary objectives of this study are to compare the two treatment groups with respect to: - Overall survival (OS); - Objective response rate (ORR) on the basis of the blinded independent central review; - Investigator assessed PFS; - Patient reported outcomes for health related quality of life; - Safety and tolerability		
Treatments groups	SYD985		Every three weeks (Q3W) with 1.2 mg/kg SYD985 291 subjects treated
	Physician's Choice (n=146)		Option 1: Lapatinib + Capecitabine 27 subjects treated Option 2: Trastuzumab + Capecitabine 24 subjects treated Option 3: Trastuzumab + Vinorelbine 47 subjects treated Option 4: Trastuzumab + Eribulin 46 subjects treated
Endpoints and definitions	Independent central review-Progression-free survival	ICR-PFS	PFS based on blinded ICR of tumour assessment according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. PFS was defined as the time from the date of randomisation to the date of first documented ICR-assessed disease progression according to RECIST v1.1 or death due to any cause (whichever occurred earlier).

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Study identifier	SYD985.002 ; EudraCT Number: 2017-001994-18 ; IND Number: 131333		
	Overall survival	OS	Time from the date of randomisation to the date of death due to any cause.
	Independent central review-Objective response rate	ICR-ORR	Proportion of patients with ICR-assessed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1.
	Investigator assessed PFS	INV-PFS	Time from the date of randomisation to the date of first documented investigator-assessed disease progression according to RECIST v1.1 or death due to any cause (whichever occurred earlier).
	Duration of response	DoR	Only applied to patients whose best overall response was CR or PR according to RECIST v1.1. The start date was the date of first documented response (CR or PR), and the end date was the date defined as first documented disease progression or death from any cause (whichever occurred first).
Database lock	31 March 2021 (PFS) 30 June 2022 (OS)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The PFS was analysed based on the data in the full analyses set (FAS) population, which included all patients who signed an ICF and were randomised. As a measure of sensitivity, efficacy analyses were also performed based on the data in the per protocol set (PPS), which included patients who were administered at least 1 dose of trial medication and who did not have any major protocol deviations. In addition, on the FAS population sensitivity analyses were performed with actual treatment received, without stratification factors, earliest progressive disease (PD) from ICR or local assessment and PD one day after last RECIST. Subgroup analyses by baseline demographics, stratification factors, and key disease characteristics were pre-specified to assess the overall consistency of efficacy results.		
Descriptive statistics and estimate variability	Treatment group	SYD985	Physician's Choice
	Number of subjects	291	146
	ICR-PFS, n (%) Median [95% CI] months	140 (48.1) 7.0 (5.4, 7.2)	86 (58.9) 4.9 (4.0, 5.5)
	Hazard ratio (95% CI)[a] p-value[b]	0.64 (0.49, 0.84) 0.002	
	OS, n (%) Median [95% CI] months	181 (62.2) 21.0 (18.1, 25.0)	94 (64.4) 19.5 (14.2, 23.1)
	Hazard ratio (95% CI)[a] p-value[c]	0.87 (0.68, 1.11) 0.236	
	ICR-ORR, n (%) [95% CI][d]	70 (27.8) [22.3, 33.7]	36 (29.5) [21.6, 38.4]
	p-value[e]	0.792	

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Study identifier	SYD985.002 ; EudraCT Number: 2017-001994-18 ; IND Number: 131333		
	INV-PFS, n (%) Median [95% CI] months	153 (52.6) 6.9 (6.0, 7.2)	103 (70.5) 4.6 (4.0, 5.6)
	Hazard ratio (95% CI) p-value	0.5995 (0.4666, 0.7703) <0.001	
Notes	CI=confidence interval, NE=not estimable a Hazard ratio calculated using the Cox proportional hazards model, stratified similarly to the log-rank test. b p-value from stratified log-rank test for median estimate of progression-free survival: stratified according to the randomisation stratification factors. c p-value from the stratified log-rank test for Kaplan-Meier estimate of median OS: stratified according to the randomisation stratification factors. d The 95% CIs were computed using the exact binomial method. e p-value from Cochran-Mantel-Haenszel test including the randomisation stratification factors.		

3.3.4.4. Clinical studies in special populations

Not applicable.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

All patients included had to have pathologically documented breast cancer that had confirmed HER2 positive expression (oestrogen receptor/progesterone receptor positive subjects may be enrolled if they are HER2 positive) according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines evaluated at a Central Laboratory. Patients must have an adequate tumour sample available for confirmation of HER2 status by Central Laboratory (based on most recent tumour tissue sample). Therefore, adequate archived or recent tumour tissue sample for HER2 testing should be obtained and the most recent tumour tissue sample should be submitted. If prior tissue specimen is submitted, document reason why most recent tumour sample is unavailable. The sample should be sent to the Central Laboratory to confirm HER2 status.

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

3.3.4.7. Supportive study (SYD985.001)

The efficacy of SYD985 monotherapy at the dose of 1.2 mg/kg IV Q3W in patients with HER2-positive unresectable locally advanced or metastatic breast cancer is mainly based on data from 437 patients enrolled in the SYD985.002 trial described above. In addition, data of Cohort A of the FIH phase I trial SYD985.001 in which 50 patients with HER2-positive breast cancer were treated with the intended dose regimen (1.2 mg/kg Q3W) are used as supportive data.

The comparative centrally assessed RECIST data from the controlled comparative SYD985.002 trial in at least third-line MBC is considered the pivotal data in this application to support the efficacy claims. In the SYD985.001 phase I trial, the RECIST data were investigator-assessed and not centrally reviewed as in the SYD985.002 trial. In addition, there were differences in the inclusion/exclusion criteria and

different populations enrolled in the two trials (e.g. regarding number of prior treatment regimens and prior pertuzumab treatment).

In the SYD985.002 trial the FAS is used for all efficacy analyses, the FAS included all patients who were randomised. In the SYD985.001 trial the FAS is used for the efficacy analyses of ORR, CBR, best overall response and DOR. PFS and OS analyses are performed with the SAS. The FAS included all patients enrolled who received at least one dose of study treatment and had at least one post-baseline RECIST assessment. The SAS included all patients enrolled who received at least one dose of study treatment. In the sections below it will be specified which population was used for the SYD985.001 trial. In the SYD985.002 trial efficacy analyses were performed with the data from baseline up to treatment discontinuation.

The disposition, demographic profile, baseline characteristics and prior systemic therapy related to trial indication of the patients in the SYD985.002 trial and Cohort A of the SYD985.001 trial is summarised in the tables below.

Table 44: Disposition of patients - SYD985.002 and SYD985.001 Cohort A

	SYD985.002			SYD985.001 Cohort A
	SYD985 N=291	Physician's Choice N=146	Total N=437	Total N=50
Patients randomized/enrolled, n (%)	291 (100)	146 (100)	437 (100)	50 (100)
Belgium	25 (8.6)	15 (10.3)	40 (9.2)	12 (24.0)
Canada	15 (5.2)	9 (6.2)	24 (5.5)	-
Denmark	7 (2.4)	3 (2.1)	10 (2.3)	-
France	46 (15.8)	22 (15.1)	68 (15.6)	-
Great Britain	43 (14.8)	16 (11.0)	59 (13.5)	24 (48.0)
Italy	50 (17.2)	20 (13.7)	70 (16.0)	-
Netherlands	3 (1.0)	0	3 (0.7)	4 (8.0)
Singapore	20 (6.9)	15 (10.3)	35 (8.0)	-
Spain	44 (15.1)	23 (15.8)	67 (15.3)	10 (20.0)
Sweden	4 (1.4)	4 (2.7)	8 (1.8)	-
United States of America	34 (11.7)	19 (13.0)	53 (12.1)	-
Patients treated, n (%)	287 (98.6)*	138 (94.5)#	425 (97.3)	50 (100)
Patients ongoing on trial drug at cutoff date for DBL, n (%)	6	2	8	Not applicable
Patients discontinued treatment, n (%)	285 (97.9)	144 (98.6)	429 (98.2)	50 (100)
Adverse event	99 (34.0)	7 (4.8)	106 (24.3)	10 (20.0%)
Non-compliance	1 (0.3)	1 (0.7)	2 (0.5)	-
Progressive disease	167 (57.4)	114 (78.1)	281 (64.3)	33 (66.0%)
Physician decision	2 (0.7)	3 (2.1)	5 (1.1)	-
Withdrawal by patient	2 (0.7)	6 (4.1)	8 (1.8)	1 (2.0)
Other	14 (4.8)	13 (8.9)	27 (6.2)	2 (4.0)
Detriment to the patient's well-being	-	-	-	4 (8.0)
Patients discontinued trial, n(%)	152 (52.2)	87 (59.6)	239 (54.7)	Not defined in dataset
Lost to follow-up	7 (2.4)	3 (2.1)	10 (2.3)	-
Withdrawal by patient	5 (1.7)	7 (4.8)	12 (2.7)	-
Death	135 (46.4)	77 (52.7)	212 (48.5)	-
Other	5 (1.7)	0	5 (1.1)	-

* In the SYD985 group 4 patients discontinued treatment directly after randomization.

\# In the physician's choice group 8 patients discontinued treatment directly after randomization. One patient in the physician's choice group received SYD985 for the duration of the trial.

SYD985.002 cutoff date for DBL = March 31, 2021

Table 45: Demographic profile of patients - SYD985.002 (FAS) and SYD985.001 Cohort A (SAS)

	SYD985.002			SYD985.001 Cohort A
	SYD985 N=291	Physician's Choice N=146	Total N=437	SYD985 N=50
Age at baseline (years)				
N	291	146	437	50
Mean (SD)	55.9 (11.20)	57.3 (10.97)	56.4 (11.13)	54.7 (11.44)
Median (range)	56.0 (24/84)	58.0 (34/86)	56.0 (24/86)	53.5 (30/80)
Gender, n (%)				
Female	291 (100)	146 (100)	437 (100)	50 (100)
Male	0	0	0	0
Race, n (%)				
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)	0
Asian	29 (10.0)	17 (11.6)	46 (10.5)	0
Black or African American	4 (1.4)	2 (1.4)	6 (1.4)	1 (2.0)
White	202 (69.4)	95 (65.1)	297 (68.0)	47 (94.0)
Other	1 (0.3)	2 (1.4)	3 (0.7)	2 (4.0)
Not disclosed	54 (18.6)	30 (20.5)	84 (19.2)	0
Ethnicity, n (%)				
Hispanic or Latino	11 (3.8)	8 (5.5)	19 (4.3)	1 (2.0)
Not Hispanic or Latino	225 (77.3)	103 (70.5)	328 (75.1)	49 (98.0)
Not disclosed	55 (18.9)	35 (24.0)	90 (20.6)	0
Childbearing potential, n (%)				
Yes	64 (22.0)	32 (21.9)	96 (22.0)	13 (26.0)
No – postmenopausal	204 (70.1)	105 (71.9)	309 (70.7)	28 (56.0)
No – Surgically sterilized	23 (7.9)	9 (6.2)	32 (7.3)	9 (18.0)
Weight, n (%)				
N	291	146	437	50
Mean (SD)	65.8 (14.1)	66.1 (16.5)	65.9 (14.9)	69.2 (14.4)
Median (range)	64.1 (28.9/111.5)	63.9 (33.1/124.3)	64.0 (28.9/124.3)	67.0 (39.1/113.2)
BMI				
N	288	145	433	48
Mean (SD)	25.14 (5.0)	25.54 (6.1)	25.28 (5.4)	25.88 (4.6)
Median (range)	24.26 (14.5/44.8)	24.46 (13.1/55.3)	24.27 (13.1/55.3)	24.42 (16.9/37.6)

Table 60: Baseline disease characteristics of patients - SYD985.002 (FAS) and SYD985.001 Cohort A (SAS)

	SYD985.002			SYD985.001 Cohort A
	SYD985 N=291	Physician's Choice N=146	Total N=437	SYD985 N=50
Time from diagnosis to trial entry (years)				
N	291	146	437	50
Mean (SD)	7.1 (5.1)	7.5 (5.9)	7.2 (5.4)	7.4 (4.8)
Median (range)	5.77 (0.7/31.3)	5.80 (0.9/30.2)	5.4 (0.7/31.3)	6.5 (2/21)
Time from LABC or MBC diagnosis to trial entry (years)				
N	291	146	437	Not defined in dataset
Mean (SD)	4.2 (2.9)	4.0 (3.4)	4.2 (3.1)	
Median (range)	3.60 (0.0/18.6)	2.93 (0.0/19.5)	3.46 (0.0/19.5)	
Disease type, n (%)				
Locally advanced	18 (6.2)	10 (6.8)	28 (6.4)	1 (2.0)
Metastatic	273 (93.8)	136 (93.2)	409 (93.6)	49 (98.0)
Metastatic sites, n (%)				
Bone	138 (47.4)	61 (41.8)	199 (45.5)	Not defined in dataset
Breast	17 (5.8)	14 (9.6)	31 (7.1)	
Hepatic lobe	95 (32.6)	43 (29.5)	138 (31.6)	
Lung	138 (47.4)	71 (48.6)	209 (47.8)	
Lymph nodes	161 (55.3)	85 (58.2)	246 (56.3)	
Skin	31 (10.7)	24 (16.4)	55 (12.6)	
Other	63 (21.6)	37 (25.3)	100 (22.9)	
Visceral disease, n (%)				
Yes	171 (58.8)	88 (60.3)	259 (59.3)	Not defined in dataset
No	99 (34.0)	49 (33.6)	148 (33.9)	
Brain metastases, n(%)				
Yes	40 (13.7)	16 (11.0)	56 (12.8)	Not defined in dataset
No	251 (86.3)	130 (89.0)	381 (87.2)	
Progesterone receptor status, n (%)				
Positive	103 (35.4)	60 (41.1)	163 (37.3)	12 (24.0)
Negative	172 (59.1)	83 (56.8)	255 (58.4)	34 (68.0)
Unknown	16 (5.5)	3 (2.1)	19 (4.3)	4 (8.0)
Estrogen receptor status, n (%)				
Positive	150 (51.5)	81 (55.5)	231 (52.9)	27 (54.0)
Negative	132 (45.4)	63 (43.2)	195 (44.6)	23 (46.0)
Unknown	9 (3.1)	2 (1.4)	11 (2.5)	0

Table 46: Prior systemic therapy related to the trial indication - SYD985.002 (FAS) and SYD985.001 Cohort A (SAS)

	SYD985.002			SYD985.001 Cohort A
	SYD985[#] N=291	Physician's Choice[#] N=146	Total[#] N=437	SYD985~ N=50
Number of prior treatment regimens, n (%)				
Mean (SD)	4.9 (2.85)	5.2 (3.02)	5.0 (2.91)	6.7 (3.60)
Median (range)	4.0 (1/16)	5.0 (1/14)	4.0 (1/16)	6.0 (1/21)
Number of prior HER2 targeting treatment regimens, n (%)				
Mean (SD)	4.0 (2.29)	4.0 (2.22)	4.0 (2.26)	Not defined in dataset
Median (range)	3.0 (1/12)	3.0 (1/11)	3.0 (1/12)	
Previous exposure to HER2-targeting therapy, n (%)				
Trastuzumab	260 (89.3)	126 (86.3)	386 (88.3)	46 (92)
Trastuzumab emtansine	255 (87.6)	128 (87.7)	383 (87.6)	40 (80)
Pertuzumab	177 (60.8)	84 (57.5)	261 (59.7)	15 (30)
Lapatinib	87 (29.9)	36 (24.7)	123 (28.1)	23 (46)
Neratinib	16 (5.5)	2 (1.4)	18 (4.1)	2 (4)
Tucatinib/Placebo*	9 (3.1)	10 (6.8)	19 (4.3)	0
Margetuximab	6 (2.1)	0	6 (1.4)	0
Trastuzumab deruxtecan	6 (2.1)	2 (1.4)	8 (1.8)	0

Table 47: Results of Efficacy trials

Trial ID	Treatm. arm	Enrolled/ Treated/ Disc. Treatm./ Disc. trial	Primary endpoint		Secondary endpoints						
			PFS ICR		PFS inv. Ass.		Overall survival		ORR ICR		QoL
			KM estimate Median (95% CI)	Hazard ratio (95% CI) P value	KM estimate Median (95% CI)	Hazard ratio (95% CI) P value	KM estimate Median (95% CI)	Hazard ratio (95% CI) P value	% responders (95% CI)	Cochran-Mantel-Haenszel test P value	MMRM analyses P value
SYD 985. 002	SYD985	291/ 287/ 285/ 152	7.0 (5.4-7.2)	0.6401 (0.4885-0.8389) 0.002	6.9 (6.0-7.2) Months	0.5995 (0.4666-0.7703) <0.001	20.4 (18.0-23.7) Months	0.8253 (0.6233-1.0928) 0.153	27.8% (22.3-33.7)	0.732	Treatm. 0.202
	Phys. Choice	146/ 138/ 144/ 87	4.9 (4.0-5.5)	-	4.6 (4.0-5.6) Months	-	16.3 (13.4-22.8) Months	-	29.5% (21.6-38.4)	-	-
Trial ID	**Treatm. arm**	**Enrolled/ Treated/ Disc. Treatm./ Disc. trial**	**Primary endpoint**		**Secondary endpoints**						
			ORR Investigator assessed		**PFS inv. Ass.**		**Overall survival**				
SYD 985. 001	Cohort A	50/ 50/ 50/ 50	33.3% (20.4-48.4)	-	7.6 (4.2-10.9) Months	-	19.2 (14.0-21.7) Months	-	-	-	-

PFS = Progression Free Survival, ICR = independent Central Review, MTD = Maximum Tolerated Dose, RP2D = Recommended Phase 2 Dose, ORR = Objective Response Rate.

3.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the new active substance trastuzumab duocarmazine (also known as SYD985, Jivadco) is primarily based on the pivotal SYD985.002 study (TULIP), which is a multicentre, randomised, open-label, phase 3 clinical trial which compared the efficacy and safety of trastuzumab duocarmazine to physician's choice (TPC) in patients with HER2+ unresectable locally advanced or metastatic breast cancer. This study was conducted at 83 sites in 11 countries (Belgium, Canada, Denmark, France, Great Britain, Italy, Netherlands, Singapore, Spain, Sweden, and United States) and the study population was predominantly comparable to the European patient population. A total of 437 patients were randomised 2:1 to the trastuzumab duocarmazine arm (n=291) and the TPC arm (n=146). Results from this pivotal trial are supported by data from the Cohort A of the FIH phase I trial SYD985.001 in which 49 patients with HER2+ breast cancer were treated with the intended dose regimen (1.2 mg/kg IV Q3W).

SYD985.001 phase I dose-finding study first tested the dose range of 0.3mg/kg to 2.4mg/kg Q3W in patients with locally advanced or metastatic solid tumours of any origin (Part I) or in patients with locally advanced metastatic breast, gastric, urothelial, or endometrial cancer (Part II). The maximum tolerated dose of SYD985 as a single agent was not reached, but 1 case of fatal pneumonitis was reported at 2.4 mg/kg, which was considered a dose-limiting toxicity. No other DLTs were observed at any other dose levels. Based on Part I results, the dose of 1.2 mg/kg was selected for further investigation in the dose expansion part (Part II) of the study. This is endorsed as there was generally no clear relationship between increased dose of SYD985 and efficacy results in particular with the primary endpoint of ORR. The Kaplan-Meier estimate of the median duration of PFS (secondary endpoint) was highest for the 1.2 mg/kg dose (42.3 weeks; 95% CI: 25.57; 48.14) also. In Part I, almost all patients experienced a treatment-related TEAEs at every dose level of SYD985 (0.3 mg/kg to 2.4 mg/kg) suggesting that the toxicity of SYD985 do not seem to be dose dependant. The severity of the events does not seem to be dose dependent either as treatment-related TEAEs with a toxicity Grade ≥ 3 were seen with inconstant proportions in the different groups of patients (i.e. 0.3 mg/kg: 0%; 0.6 mg/kg: 0%; 1.2 mg/kg: 83.3%; 1.5 mg/kg: 16.7%; 1.8 mg/kg: 25.0%; 2.4 mg/kg: 25.0%). The majority belonged to the SOCs eye disorders. The majority of patients with at least one related TEAE with a toxicity Grade ≥ 3 was in the 1.2 mg/kg (5 of 13 patients, 38.5%) group. However, it is agreed that these results should be read in parallel with patient exposure duration (longer in the 1.2 mg/kg group in the FAS and breast cancer patients). In Part II, almost all breast cancer patients experienced a treatment-related TEAEs (98.0%), balanced between cohorts (A1, A2 and A3). The frequency of patients with drug-related TEAEs of intensity Grade 3 or higher was lower in the Cohort A1 (23.5%) versus the Cohort A2 (41.2%) and A3 (25.0%). The 3-week interval regimen is also agreed. The MAH provided supportive data on the chosen

dose reduction scheme from 0.9 mg/kg to 0.6 mg/kg given the very limited efficacy results and benefit observed in the phase I study at 0.6 mg/kg dose. No clear benefit was observed for patients treated with SYD985 at the dose of 0.6 mg/kg in the SYD985.001 phase I dose-finding study (stable disease as best overall tumour response with a majority of patients experiencing progression). Very few patients were treated at this dose (dose escalation, n=3; dose expansion, n=2 patients with dose reduced to 0.6mg/kg). Dose reduction discussion is of importance in this context since SYD985 causes toxicities that should be managed by dose reduction. As requested, the MAH has provided data from SYD985.002 pivotal study to better characterise patient response to SYD985 at reduced dose. 20/23 patients (86.9%) treated at the reduced dose of 0.6 mg/kg discontinued treatment for disease progression or physician decision i.e. benefit/risk no longer considered favourable without a particular AE indicated as primary reason (9/20; 45.0%) or AE (11/20; 55.0%). Half of the patients received only 1 cycle of SYD985 0.6 mg/kg and the majority of patients (70.0%) received ≤5 cycles of treatment. 3 patients were still ongoing on treatment at the time of the cut-off. Combined in both trials, dose reduction to 0.6 mg/kg allowed 25 patients to continue treatment for a median of 1 cycle (median 1, min/max 1-26). Some patients deriving a benefit for an extended period of time. It is acknowledged that to some extend patients could benefit from this reduced dose with limited toxicity or will be able to switch rapidly to another line of HER2 based regimen if not. A warning should be added to the SmPC. Please also refer to the PK assessment discussion.

The overall design of the pivotal phase III TULIP study is endorsed. Physician's choice therapy options are agreed as they were the main standard of care treatments during study conduction. It is well noted that concurrent developments were ongoing for tucatinib in association with trastuzumab and capecitabine (HER2CLIMB study) and T-DXd monotherapy from the third line setting (Destiny-Breast 01) at the time of TULIP conduction. This situation, although understandable, precludes any positioning of trastuzumab duocarmazine over these therapies. In clinical practice several factors will interfere for positioning of the concurrently available but not-directly compared treatment options, including the CNS involvement, safety profile and evidence supporting the potential to overcome resistance mechanisms.

A ratio of 2:1 instead of 1:1 was chosen to increase the number of patients treated with trastuzumab duocarmazine in order to collect more data on the safety profile of the drug. Per the sample size calculations, the number of patients in the TPC group was sufficient to show a significant difference in efficacy between the treatment groups. The unbalanced 2:1 randomisation ratio is acceptable. Treatments used in the control group were sufficiently known and there was no need to balance the two trial arms. Stratification of geographical region was included to assure that any geographical differences in type of prior treatments and concomitant medication is evenly divided. This is endorsed. Stratification of the number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (1 or 2 and > 2) was performed. As patients with more extensive prior treatments may respond differently to SYD985 due to these prior treatments the choice of this stratification factor is important and agreed. However, pooled results for 2L and 3L patients should have been separated to better quantify the clinical benefit for the 2L patients specifically as this particular patient population is claimed in the indication (2nd bullet point). The MAH provided unpooled results (see discussion below). Prior treatment with pertuzumab (yes and no) was also included as a stratification factor which is endorsed.

Patients included in TULIP were women with unresectable locally advanced or metastatic HER2+ breast cancer, who received in the non-curative setting at least two HER2-targeting treatment regimens OR T-DM1. The inclusion of female participants only is questionable since breast cancer can also affects men. However, the results from this pivotal trial are considered extrapolatable to men with HER2+ metastatic breast cancer in line with previous EMA decisions for HER2-targeted treatments. According to T-DM1 SmPC patients may receive T-DM1 as 1st line therapy of unresectable locally advanced or metastatic breast cancer following early failure (<6 months) of adjuvant treatment with trastuzumab and a taxane,

separately or in combination. It is understood that these patients (2L) were eligible for participation in TULIP according to inclusion criteria 3. The applicant clarified that only 8 (2.7%) and 13 (8.9%) patients in the SYD985 and TPC groups were 2L patients respectively. These low numbers preclude any meaningful subgroup analysis. No conclusion can be made for this specific claimed population (second bullet point of the indication). As mentioned above, it is noted that this patient population could be considered to have poorer diagnosis and outcome since they early progressed on HER2 targeting therapy adjuvant treatment.

Overall, SYD985.002 included a heterogeneous albeit rather late-line population with a median of prior treatment received of 3 (1-12). It is also noted that recommendations for HER2+ metastatic breast cancer have evolved, notably with T-DXd now representing the standard of care over T-DM1 where available in the EU following Destiny- Breast03 results and the extension of its marketing authorisation the 11 July 2022 (EMEA/H/C/005124/II/0014).

Given the concurrent development of T-DXd 2L with SYD985, patients in TULIP did not receive T-DXd prior to inclusion. The benefit risk balance of SYD985 following a treatment with T-DXd is not assessable since no data on how the IMP performs after 2L T-DXd specifically is available. This counts as an uncertainty.

To be noted, only patients with no evidence of brain metastases or stable brain metastases were included. Patients had measurable or non-measurable disease that is evaluable per Response Evaluation Criteria for Solid Tumours (RECIST version 1.1). Patients included had centrally confirmed HER2-positive expression according to the guidelines from the American Society of Clinical Oncology, which is standard for clinical trials and endorsed. Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 were included, in line with the intended heavily pre-treated population included in the study. Extrapolation to patients with ECOG>2 (exclusion criterion) is acceptable in line with previous EMA decisions.

In the treatment setting considered, i.e. rather late-line treatment of metastatic HER2+ breast cancer, the prognosis of patients is generally poor with short PFS and OS. In TULIP, the median PFS and OS (Kaplan-Meier estimates) was 4.9 months (4.0 – 5.5) and 19.5 months (14.2, 23.1) in the TPC group respectively. In this setting, OS would have been the most preferable and feasible primary endpoint. However, it is acknowledged that PFS could be an acceptable primary endpoint as already agreed for another HER2-targeted therapy procedure in this setting and as discussed in previous scientific advice. The proposed primary endpoint PFS is considered acceptable provided that a detrimental effect of the treatment on overall survival can be ruled out. Of important note, the applicant did not raise the OS secondary endpoint to the level of a key secondary endpoint, in deference of the SAWP advice given.

Considering the open label design of TULIP, ICR assessed PFS as primary endpoint over investigator assessed PFS is endorsed. ORR is considered a valuable and important secondary endpoint in this confirmatory study, as well as other critical endpoints including survival, safety and quality of life. The collection of PRO data is acknowledged in this late stage setting where improving patient quality of life is of great relevance. Patient's symptoms, functioning, and overall well-being were measured with the validated, self-reported questionnaires of the EORTC which is acceptable. However due to the open-label design prone to bias presented PRO data are therefore considered supportive only.

One point of unclarity was the fact that between Protocol version 6 and 7 the drop out assumptions used for the sample size calculation were adapted upwards following the pre-planned interim evaluation by the DMC. An average of 20% drop out in the physician's choice group and 30% in the SYD985 group was initially assumed and revised to average of 30% drop out in the physician's choice group and 40% in the SYD985 group. The applicant was also requested to discuss the reasons for performing the PFS analysis earlier than initially planned and how this may impact the study integrity as well as the result. The applicant clearly and extensively commented and described the population sample size calculations

as per amendments 6 and 7. There is minor impact when the PFS analysis is performed at the primary analysis time point or at the final OS analysis time point.

A major protocol deviation was documented for 18.9% of patients in the SYD985 group compared with 13.7% of patients in the physician's choice group. The most common major protocol deviations were categorised under eligibility criteria (for 47 of 75 patients with major protocol deviations), balanced between SYD985 and TPC arms (10.7% versus 11.0% respectively), and under reporting of SAEs ("Adverse events and therapy": 21 of 75 patients with major protocol deviations) which caused the greatest imbalance in the observed protocol deviations between SYD985 and TPC arms (6.9% versus 0.7% respectively). This may have been caused by the open-label design combined with a new treatment versus well-known treatments effect, but nonetheless the consequences on the safety of this imbalance are of important interest in light of the other safety issues noted and discussed later. The MAH clarified that all events were reported, with some delay, and were included in the analyses. It is agreed that the overall analyses of all AEs, SAEs and AESIs reported in the trial are not affected by this delay in reporting.

Efficacy data and additional analyses

A total of 437 patients were randomised in TULIP. 291 patients (39%) were screen failures which is considered a high proportion of screened patients. The main reason of screen failure was related to inclusion criterion 4 defining the central confirmation of the HER2 status (26.5% of patients who failed screening). No issue was raised on this particular point given the importance of HER2 status confirmation to treat patients with Jivadco. Second reason of screen failure was related to exclusion criterion related to brain metastases (23.4%). Patients with BM subgroup is of importance given the late-line population included in TULIP. Of note, SmPC section 5.1 indicates that only patients with stable/non-symptomatic BM were treated with Jivadco in TULIP.

There were no imbalances in the disease characteristics that are considered to have had a major impact on the study results. Of the 437 women randomised in the FAS the majority was white (68.0%) or Asian (10.5%) with a median age of 56 years (range 24 to 86) and ECOG PS 0 or 1 (52.5% and 43.9% respectively). The median time from unresectable locally advanced or MBC diagnosis to trial entry was 3.46 years. There were 28 patients (6.4%) with unresectable locally advanced disease and 409 patients (93.6%) with metastatic disease. Metastases were mainly found in the lymph nodes (56.3%), lungs (47.8%) and bones (45.5%). A total of 12.8% of the patients included had brain stable metastases. More than half of the patients included (n=244, 58.2%) were also positive for the hormone receptor status (HR+) and 59.3% of the patients had visceral disease.

The majority of the patients (58.8%) received 3 or more prior HER2 targeting treatment regimens in the metastatic setting before the inclusion in the study (with a median of 3 [range 1 to 12]). In the setting of a clinical trial and testing a new drug substance, it is acceptable that the included patients were more heavily pre-treated than the targeted patient population, as long as they have received available standard of care, which was the case at the time of study conduction. However, it is important to note that the comparator arm had a higher proportion of very heavily pre-treated patients included (5+ lines prior; all treatment regimen and settings [for early and metastatic breast cancer] considered), amounting to +6.3%. The largest differences however seem to be located in the 3-4 and 5-8 prior lines subgroups, which incidentally also represent the subgroups covering the largest amount of trial participants (a relative difference of -8.7% and +6,1% respectfully versus the IMP arm). Median number of prior treatment regimens in the metastatic setting was 5 (1-14) and 4 (1-16) respectively for TPC and SYD985 arms. These combined divergences may imply that overall the comparator group was clinically worse off in regards to the state of their disease, and hence there may have been a measure of positive bias effect towards the IMP outcomes. The MAH should provide a multivariate analysis of PFS incorporating the variable prior line of treatment to neutralise the observed imbalance between both arms (more pre-treated patients in the TPC group) (**OC**). From data provided, it is interesting to observe

that the advantage with SYD985 is more pronounced for more heavily pre-treated patients. However, it is agreed that these results should be considered with caution given the small number of responders.

It is noted that a total of 11.7% and 12.4% of the patients included did not receive trastuzumab and/or T-DM1 in the metastatic setting prior to inclusion. The MAH confirmed that these therapies were received as adjuvant therapies (excluding 2 deviating patients). Treated patients received trastuzumab and/or T-DM1 in adjuvant or metastatic setting. Only 8 patients (1.8%) received T-DXd prior to inclusion which is understandable and acceptable since T-DXd in the 2L setting was not the SOC at the time of TULIP conduction.

After a median follow-up of 6.8 months (95% CI 5.6, 7.0) in the SYD985 group and 7.8 months (95% CI 5.5, 9.7) in the physician's choice group, 48.1% and 58.9% of patients had an event (progression or death) respectively. The primary endpoint of PFS by IRC was statistically significantly improved with SYD985 by 2.1 months in the FAS population, i.e. from 4.9 months to 7.0 months (HR 0.6401 (95%CI: 0.4885; 0.8389), p-value=0.002). Investigator-assessed PFS as secondary endpoint also supports this (HR=0.5995 (95%CI: 0.4666, 0.7303, p-value <0.001). In that sense it is agreed that the primary endpoint is met. It should be noted however that the investigator-assesses PFS outcomes are directionally congruent but also seemingly indicate a much larger treatment effect compared to the IRC-assessed outcomes. This may indicate that in this open-label trial investigators were subject to a bias pressure and in that sense, it is reassuring that the primary endpoint was IRC-assessed. The clinical relevance of the statistically significant median IRC-PFS improvement of 2.1 months with trastuzumab duocarmazine compared to SoC is questioned in the context of all available data. It is not excluded that the observed magnitude is overestimated (see below).

The applicant provided clarifications on the way disease progression was documented in patient censored after treatment discontinuation. It is confirmed that disease progressions were documented after the patient discontinuation based on all available information, scans included (if available), even though they were not anymore required after the discontinuation. A basic description of reasons (split in "all reasons" and "toxicity") that led to censor patients according to investigators was provided for both arms. However, it is confirmed that after discontinuation, patients were not monitored as effectively as during treatment, which to some extent is understandable. Nevertheless, this led to less accurate or missing data being collected, which may have had an impact on the PFS estimation.

In order to investigate the hypothesis that treatment discontinuation is not an informative censoring factor, the applicant has provided additional sensitivity analyses for the ICR- and investigator-assessed PFS. For the investigator PFS, all disease progressions observed between treatment discontinuation and the cut-off dates considered (March 31, 2022 and June 30, 2022) were taken into account. The reduction in the risk of progression resulting from these analyses is in line with that of the main analysis. Three other approaches were also proposed, focusing on patients who discontinued their treatment due to toxicity and addressing the censor according to different logical rules:

- worst case scenario: patients in the SYD arm censored for discontinuation of treatment due to toxicity were considered to have developed PD at the date of the visit at which discontinuation of treatment was observed; for the same patients in the control arm, they were censored at the cut-off date considered in these analyses (March 31, 2022);

- early progression scenario: all patients censored for discontinuation of treatment due to toxicity (SYD and control arms) were considered to have PD at the date of the visit when treatment was stopped;

- disease progression at the cut-off date scenario: all PD initially censored at the date of treatment discontinuation for toxicity are censored at the cut-off date.

All these complementary approaches have increased significantly the number of true progression events accounted for in both arms, ending up in more events in the SYD arm than in the control arm. Only the

last scenario (PD at cut-off date) considering true dates of PD before the cut-off, gave favourable hazard ratios close to the primary analysis for ICR PFS and local PFS. The other two approaches (worst case scenario and early RFP) provided conflicting results from the primary analysis. Unlike in the PD at cut-off date scenario, these scenarios set a disease progression at the date of the treatment discontinuation so that even the actual progression dates are replaced by earlier ones. These approaches have more affected the SYD985 arm due to its higher number of events, mechanically reducing the median of progression-free survival drastically in that arm. Even if these two scenarios seem less realistic, they tend to indicate that discontinuing treatment might be informative in that trial, contributing to the uncertainty of PFS estimation.

The tipping-point analysis approach used by the applicant to investigate the censoring process has provided additional information. This approach consisted in exploring the assignment of disease progressions at various time-points to fractions of patients (35% to 85%) who had discontinued treatment due to toxicity. Time-points explored for the disease progressions started from the censoring date (as in early PD scenario) to which were successively added 1 month, 1.5, 2, 2.5 and 3 months. These analyses showed that the higher the fraction of patients concerned and the closer the disease progression date was to the censorship date, the lower the risk of progression reduction. In agreement with the applicant, it seems unlikely that patients would experience progression of the disease as soon as they stopped treatment or shortly after. From these analyses, the more consistent results with the primary analysis are for disease progressions occurring 2 to 3 months after the discontinuation in the smallest fraction of patient imputed (35%). Although this analysis shows that conditions of data imputation should be a bit extreme to reverse the observed positive outcome of the primary analysis, this does not definitively dissipate the uncertainties on the PFS estimation. It is difficult to believe that treatment discontinuation has little or no impact on progression-free survival and overall survival. This is even more difficult in view of the large difference in treatment discontinuation due to toxicity in the SYD985 group (34% versus 5% in the control group) and the lightened conditions of patient monitoring after treatment discontinuation.

Regarding the duration of patient follow-up in the study, it is true that the size of the control arm workforce reduces the accuracy of the estimates. However, within the trial, the actual follow-up median of SYD arm patients was 1 month shorter in this arm, which is not negligible compared to the actual 2 months of survival median with no progression observed in the same arm as compared to the control arm. This adds uncertainty to the robustness of the observed PFS results (see major objections).

OS is considered as an important endpoint to assess SYD985 clinical benefit in this late line population. The applicant did not raise the OS secondary endpoint to the level of a key secondary endpoint, in deference of the SAWP advice given. An update of the overall survival analysis with an additional 15-month follow-up (June 30, 2022) compared to the previous one (March 31, 2021) was provided. Both analyses gave consistent results, but still showed crossing survival curves. The OS curves and corresponding hazard ratio showed a non-significant trend towards prolonged OS in the SYD985 group compared with the physician's choice group (hazard ratio (95% CI): 0.8680 (0.6760, 1.1145), p=0.236). The Kaplan Meier curves of the 2 arms crossed each other which might suggest that at some point there might be an increased risk of death on SYD985. In order to explore the Kaplan-Meier crossover, the applicant proposed approaches exploring several periods of time in the survival curves. The Fleming Harrington / max-combo approach explores the logrank giving alternatively more weight to early, intermediate and late events so that when they are combined with the unweighted logrank, it gives treatment effect estimates and p-values. In the two other approaches (RMST and the Cox model), the applicant segmented the survival curves in three disjunctive periods of follow-up time (less than 4 months, 4 to 12 months and more than 12 months). Free from the assumption of a constant risk ratio over time, these methods allowed to average the treatment effect over the segmented periods of time. For the analysis of the two databases (March 2021 and June 2022), all three methods provided consistent

results over the whole time course and showed that there would be no detrimental effect on survival in the SYD arm as compared to physician choice. However, these methods expressed the treatment effect on different measure. Indeed, for the max combo approach, the treatment effect was expressed as a z-score while it could have been expressed as a weighted HR, more convenient for clinical interpretation. The two other approaches had more straightforward treatment effect interpretation, the difference in survival months and the hazard ratio respectively for the restricted mean survival time and the Cox model. When considering the 3 time periods separately, RMST and Cox model methods showed disturbing results in the intermediate period. Indeed, in both database analyses, patients appeared to have shorter survival times in the SYD arm than in the control arm, this detrimental effect increasing in the June 2022 database: 1 month survival reduction in the RMST approach (95% CI: [-1.9; 0.12]) and 61% increased risk of death all-cause in the Cox model approach (95% CI: [1.04; 2.50]). This unfavourable part of the survival curves jeopardises the treatment effect interpretation for the whole follow-up time course.

Regarding subgroups, HR point estimates of PFS were consistently below 1 for each defined sub-populations supporting the primary efficacy analysis for PFS, with the exception of ECOG 2. However, the results for specific subgroup are considered with caution due to the low number of patients in this subgroup leading to high uncertainty in the point estimate. An updated forest plot of OS was provided (final OS data; DCO 30 June 2022). Of note, the HR OS point estimate was below 1 for this specific subgroup (ECOG 2). The point estimate for HR+ patients (n=244, 55.8% of patients) was, with the updated analysis, below 1 with 95% CI overlapping with the HR- patient population, which is reassuring. For patients with brain lesions at screening and patients in the 2nd/3rd line setting consistent results were observed compared to results of the previous DCO. For 2/3L subgroup, it is agreed that the confidence interval was wide and the p-value was not significant (p=0.079) and subsequent treatments could have impacted OS results. A total of 56 patients included (12.6%) had stable/non-symptomatic brain lesions at screening. This low number is considered not sufficient to give any recommendation on this particular subgroup. In TULIP study, development of de novo brain metastases (BM) was low and seemed comparable between both treatment groups: 10 (3.4%) SYD985 patients and 2 (1.4%) physician's choice patients developed de novo BM. The risk of progression in the brain lesion that was present at baseline seemed also similar for SYD985 and PC treated patients (progression in a non-target brain lesion per ICR: 0.7% versus 1.4% for SYD985 and TPC group respectively). However, these numbers were small and should be interpreted with caution. No formal conclusion can be done. Given the observed final OS data results in this particular subgroup this adds uncertainties on the benefit-risk balance for Jivadco in the claimed indication, which could include patients with BM. Subgroup analyses should be mentioned in the SmpC of Jivadco (**OC**).

The ORR was numerically lower in the SYD985 arm (27.8%) than in the PC's arm (29.5%). This difference was not statistically significant (p-value=0,732). A comparable proportion of patients who had measurable disease achieved confirmed complete response (CR) ICR assessed between the two treatment arms (2.0% versus 0.8% respectively) as well as patients who achieved confirmed partial response (PR) ICR assessed (18.3% versus 20.5% respectively).

The collection of PRO data is acknowledged in this specific late line setting and specifically by using the specific and validated EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. However due to the open-label design prone to bias, presented PRO data are considered difficult to interpret. The transformed overall mean global health status score of the EORTC QLQ-C30 questionnaire at baseline was 64.5 in the SYD985 group and 62.4 in the Physician's choice group. The scores decreased (indicating a worsening) to 54.3 in the SYD985 group and 54.8 in the Physician's choice group at the end of treatment. Observations are applicable to other sub-score of the questionnaire. Global health status/QoL scale scores tended to decline from baseline to Cycle 15 in both treatment groups. No noteworthy differences between both treatment groups were seen. With increasing cycle number, the standard error and CI

increased, explained by the decline in the number of patients still on study. It is not clear however from the provided data whether ocular toxicity, fatigue and/or other safety issues could have impacted PROs.

Median DOR (Kaplan-Meier estimates) was 15.1 months in the SYD985 group and 4.6 months in the physician's choice group based on central review data. Results from local review were 6.9 months (SYD985) and 4.4 months (physician's choice). These results did not change at the secondary analysis after longer follow-up. This analysis was based on a small subset of patients (about 25% or less of patients in the FAS) who first had documented tumour response and then progressed or died. These results are not robust and should be interpreted with caution.

The CBR (ICR assessed) was 38.5% in the SYD985 group and 32.2% in the physician's choice group (local review: SYD985, 35.4%; physician's choice, 28.8%). From provided data, it is understood that compared to TPC, the majority of patients treated with SYD985 experienced stable disease as clinical benefit (47.6% of patients in SYD985 and 36.9% in TPC group) with all other criterions (CR, PR, PD) considered similar in both groups. It is acknowledged that maintaining a stable disease at this line of treatment could be of relevance. However, this should be analysed in the context of all available data. This informs discussions related to benefit-risk ratio and the safety profile of Jivadco.

Because of the high number of censored patients in both treatment groups (>74% of patients in both treatment groups did not have a response), a median Kaplan-Meier estimate of TTR could not be determined in both treatment groups for response data assessed by ICR and in the physician's choice group for local review data. Therefore, interpretation of median TTR is not possible.

Results from TULIP are supported by data from the Cohort A of the FIH phase I trial SYD985.001. A total of 50 patients were enrolled and treated in the Cohort A of the FIH trial SYD985.001. The FAS population included 49 patients. After the evaluation of the baseline data of TULIP and Cohort A of the SYD985.001 trial, it is agreed that the patient populations are comparable. It is agreed that efficacy data from Cohort A can be used as supportive data. Efficacy results (INV-PFS, OS and INV-ORR) between SYD985.001 and SYD985.002 are comparable which is reassuring. No concern is raised.

3.3.6. Conclusions on clinical efficacy

The magnitude of the median PFS improvement of 2.1 months with trastuzumab duocarmazine compared to SoC is questioned given its potentially overestimated magnitude with no impact on secondary outcomes of OS and confirmed ORR per ICR (see major objections).

3.3.7. Clinical safety

3.3.7.1. Patient exposure

The median duration of exposure to SYD985 was 4.8 months in the SYD985.002 phase III trial. A total of 101 patients (35%) had a SYD985 treatment duration of more than 6 months, with 17 patients (5.9%) more than 1 year. The median duration of exposure in Part II of the SYD985.001 trial in which patients were dosed with 1.2 mg/kg SYD985 was 4.0 months, with longest median duration in Cohort A (HER2-positive breast cancer) of 6.5 months.

In the TULIP study, the median relative dose intensity was 95.8%, with 77% of patients having had at least 85% of the planned dose of 1.2 mg/kg SYD985 Q3W.

Table 48: Extent of SYD985 exposure in completed and ongoing trials (SAS)

Parameter	SYD985.002 (TULIP) HER2-positive breast cancer 1.2 mg/kg N=288	SYD985.001		SYD985.003 Endometrial cancer 1.2 mg/kg N=53	SYD985.004 Part 1 Solid tumors 0.9 to 1.2 mg/kg N=30
		Part I Solid tumors 0.3 to 2.4 mg/kg N=39	Part II Breast, gastric, endometrial, urothelial cancer 1.2 mg/kg N=146		
Number of cycles started					
N	288	39	146	53	30
Mean (SD)	7.4 (4.94)	5.3 (3.39)	6.3 (4.53)	6.6 (4.29)	6.2 (4.96)
Median (min/max)	6.5 (1/30)	4.0 (1/16)	5.0 (1/23)	6.0 (1/17)	4.0 (1/19)
Number of cycles started, n (%)					
1-4	100 (34.7)	20 (51.3)	63 (43.2)	23 (43.4)	16 (53.3)
>4	188 (65.3)	19 (48.7)	83 (56.8)	30 (56.6)	14 (46.7)
Exposure duration (months) [1]					
N	288	39	146	53	30
Mean (SD)	5.5 (3.79)	3.9 (2.58)	5.0 (4.57)	5.0 (3.25)	4.6 (3.52)
Median (min/max)	4.8 (1/23)	3.5 (1/11)	4.0 (1/32)	4.9 (1/12)	3.2 (1/13)
Exposure duration (months), n (%) [1]					
0 - ≤3	93 (32.3)	18 (46.2)	56 (38.4)	23 (43.4)	13 (43.3)
3 - ≤6	94 (32.6)	15 (38.5)	48 (32.9)	10 (18.9)	10 (33.3)
6 - ≤9	62 (21.5)	3 (7.7)	24 (16.4)	12 (22.6)	3 (10.0)
9 - ≤12	22 (7.6)	3 (7.7)	10 (6.8)	8 (15.1)	2 (6.7)
12 - ≤24	17 (5.9)	0	6 (4.1)	0	2 (6.7)
>24	0	0	2 (1.4)	0	0
Patient years of exposure	131.6	12.8	61.2	22.0	11.5
Total dose (mg)					
N	288	39	146	53	30
Mean (SD)	536.4 (317.54)	480.5 (315.88)	500.5 (315.55)	561.8 (396.59)	395.7 (312.98)
Median (min/max)	500.7 (55/2099)	465.0 (64/1387)	450.9 (51/1479)	488.0 (72/1517)	277.8 (65/1209)
Dose delayed, n (%) [2]					
Yes	114 (39.6)	13 (33.3)	61 (41.8)	20 (37.7)	13 (43.3)
No	174 (60.4)	26 (66.7)	85 (58.2)	33 (62.3)	17 (56.7)
Dose reduced, n (%) [2]					
Yes	81 (28.1)	7 (17.9)	30 (20.5)	8 (15.1)	4 (13.3)
No	207 (71.9)	32 (82.1)	116 (79.5)	45 (84.9)	26 (86.7)
Dose modification, n (%) [2,3]					
Yes	132 (45.8)	13 (33.3)	65 (44.5)	23 (43.4)	15 (50.0)
No	156 (54.2)	26 (66.7)	81 (55.5)	30 (56.6)	15 (50.0)
Dose intensity (mg/kg/3 weeks) [4]		Not calculated	Not calculated	Not calculated	Not calculated
N	281				
Mean (SD)	1.10 (0.121)				
Median (min/max)	1.15 (0.63/1.23)				
Relative dose intensity (%) [5]		Not calculated	Not calculated	Not calculated	Not calculated
N	281				
Mean (SD)	91.8 (10.06)				
Median (min/max)	95.8 (53/103)				
Relative dose intensity, n (%) [5]		Not calculated	Not calculated	Not calculated	Not calculated
>95%	164 (56.9)				
85% - 95%	57 (19.8)				
<85%	60 (20.8)				
Unknown	7 (2.4)				

Note: cut-off date for ongoing trials SYD985.003 and SYD985.004 was October 8, 2021
[1] Exposure duration is calculated as [(last treatment date – first treatment date) +22]/30.5 (months)
[2] A patient is only counted once. If there was any dose delay or dose reduction a patient was counted as 'Yes'
[3] Dose modification is dose delayed and/or reduced
[4] Dose intensity is the ratio of dose received in mg/kg and exposure duration of 3 weeks (mg/kg/3 weeks)
[5] Relative dose intensity is calculated as 100%*(mg/kg/3 weeks)/1.2

3.3.7.2. Adverse events

An overall summary of the TEAEs reported in all 4 clinical trials with SYD985 is presented in Table below.

Table 49: Overall summary of TEAEs (SAS)

	SYD985.002		SYD985.001 N=185 n (%)	SYD985.003 N=53 n (%)	SYD985.004 N=30 n (%)
Number of patients	**SYD985 N=288 n (%)**	**Physician's choice N=137 n (%)**			
Treatment-emergent AEs (TEAEs)	278 (97)	132 (96)	185 (100)	46 (87)	29 (97)
Serious TEAEs	53 (18)	12 (9)	77 (42)	8 (15)	6 (20)[b]
TEAEs leading to death	6 (2)	0	1 (1)	4 (8)	0[b]
TEAEs leading to treatment discontinuation (either 1 drug or both drugs in PC group)	102 (35)	14 (10)	40 (22)	10 (19)	4 (13)
TEAEs leading to dose modifications[a]	132 (46)	74 (54)	91 (49)	25 (47)	12 (40)
TEAEs of grade ≥3	152 (53)	66 (48)	110 (59)	23 (43)	14 (47)
AESIs	100 (35)	1 (1)	NA[c]	10 (19)	6 (20%)
Treatment-related TEAEs	262 (91)	122 (89)	177 (96)	39 (74)	28 (93)
Treatment-related serious TEAEs	25 (9)	6 (4)	26 (14)	1 (2)	2 (7)[b]
Treatment-related TEAEs leading to death	4 (1)	0	1 (1)	0	0[b]
Treatment-related TEAEs leading to treatment discontinuation (either 1 or both drugs in PC group)	95 (33)	9 (7)	40 (22)	5 (9)	3 (10)
Treatment-related TEAEs leading to dose modifications[a]	111 (39)	68 (50)	74 (40)	21 (40)	8 (27)
Treatment-related TEAEs of grade ≥3	115 (40)	50 (36)	64 (35)	10 (19)	8 (27)
Treatment-related AESIs	98 (34)	1 (1)	NA[c]	9 (17)	6 (20%)

Note: cut-off date for ongoing trials SYD985.003 and SYD985.004 was October 8, 2021

[a] This includes dose delays and dose reductions, and for trial SYD985.001 also infusion rate reduced and/or infusion interrupted

[b] A fatal case of pneumonitis occurred 1 day after the cut-off date and is not included in the numbers

[c] AESIs were not defined in the SYD985.001 trial

TEAEs occurring in ≥10% of patients in either treatment group in Phase 3 study SYD985.002 (TULIP) are summarised in Table 65.

Table 50: TEAEs occurring in ≥10% of patients in either treatment group in SYD985.002 trial (SAS)

System Organ Class Preferred Term	SYD985 N=288 n (%)		Physician's Choice N=137 n (%)	
	All	Related	All	Related
Patients with at least 1 TEAE	278 (96.5)	262 (91.0)	132 (96.4)	122 (89.1)
Eye disorders	**225 (78.1)**	**214 (74.3)**	**40 (29.2)**	**20 (14.6)**
Conjunctivitis	110 (38.2)	102 (35.4)	3 (2.2)	1 (0.7)
Keratitis	110 (38.2)	108 (37.5)	11 (8.0)	3 (2.2)
Dry eye	87 (30.2)	82 (28.5)	14 (10.2)	10 (7.3)
Lacrimation increased	53 (18.4)	48 (16.7)	2 (1.5)	2 (1.5)
Blepharitis	36 (12.5)	32 (11.1)	2 (1.5)	0
Punctate keratitis	32 (11.1)	29 (10.1)	3 (2.2)	2 (1.5)
General disorders and administration site conditions	**182 (63.2)**	**143 (49.7)**	**79 (57.7)**	**62 (45.3)**
Fatigue	96 (33.3)	81 (28.1)	41 (29.9)	35 (25.5)
Asthenia	58 (20.1)	47 (16.3)	23 (16.8)	18 (13.1)
Gastrointestinal disorders	**179 (62.2)**	**121 (42.0)**	**91 (66.4)**	**74 (54.0)**
Nausea	73 (25.3)	55 (19.1)	43 (31.4)	34 (24.8)
Diarrhoea	60 (20.8)	31 (10.8)	49 (35.8)	41 (29.9)
Constipation	57 (19.8)	25 (8.7)	24 (17.5)	13 (9.5)
Vomiting	36 (12.5)	20 (6.9)	23 (16.8)	15 (10.9)
Stomatitis	24 (8.3)	21 (7.3)	17 (12.4)	15 (10.9)
Skin and subcutaneous tissue disorders	**134 (46.5)**	**110 (38.2)**	**60 (43.8)**	**55 (40.1)**
Alopecia	62 (21.5)	56 (19.4)	16 (11.7)	15 (10.9)
Skin hyperpigmentation	32 (11.1)	30 (10.4)	1 (0.7)	1 (0.7)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.7)	2 (0.7)	32 (23.4)	32 (23.4)
Respiratory, thoracic and mediastinal disorders	**124 (43.1)**	**63 (21.9)**	**46 (33.6)**	**15 (10.9)**
Cough	48 (16.7)	9 (3.1)	14 (10.2)	1 (0.7)
Dyspnoea	42 (14.6)	17 (5.9)	17 (12.4)	3 (2.2)
Infections and infestations	**120 (41.7)**	**38 (13.2)**	**51 (37.2)**	**22 (16.1)**
Urinary tract infection	25 (8.7)	8 (2.8)	14 (10.2)	1 (0.7)
Nervous system disorders	**106 (36.8)**	**69 (24.0)**	**50 (36.5)**	**34 (24.8)**
Headache	33 (11.5)	14 (4.9)	16 (11.7)	8 (5.8)
Investigations	**98 (34.0)**	**65 (22.6)**	**44 (32.1)**	**31 (22.6)**
Weight decreased	29 (10.1)	19 (6.6)	2 (1.5)	1 (0.7)
Neutrophil count decreased	14 (4.9)	12 (4.2)	14 (10.2)	14 (10.2)
Musculoskeletal and connective tissue disorders	**94 (32.6)**	**30 (10.4)**	**46 (33.6)**	**16 (11.7)**
Arthralgia	31 (10.8)	7 (2.4)	11 (8.0)	3 (2.2)
Metabolism and nutrition disorders	**86 (29.9)**	**44 (15.3)**	**30 (21.9)**	**20 (14.6)**
Decreased appetite	61 (21.2)	41 (14.2)	15 (10.9)	12 (8.8)
Blood and lymphatic system disorders	**74 (25.7)**	**62 (21.5)**	**44 (32.1)**	**38 (27.7)**
Anaemia	41 (14.2)	32 (11.1)	17 (12.4)	14 (10.2)
Neutropenia	31 (10.8)	31 (10.8)	33 (24.1)	29 (21.2)

Note: AEs were coded using MedDRA version 23.1

Among the SOC that were reported at a lower rate (<10%) in the phase 3 study, it is noticed an imbalance across the two treatment arms for the **cardiac disorders,** i.e. 10.1% vs 1.5% for TEAEs and 3.8% vs 0.7% for treatment-related TEAEs in the SYD985 arm and the physician's choice arm, respectively. There was higher reported tachycardia (2.4% vs 0.7%) and sinus tachycardia AEs (1.4%

vs 0) and the larger averaged mean heart rate change from baseline in the SYD985 group compared to the Physician's choice treatment groups in the ECG analysis.

TEAEs by severity (CTCAE grade)

Table 51: TEAEs by System Organ Class, Preferred Term, and Maximum severity of Grade 3 or higher occurring in >2% of patients in either treatment group in SYD985.002 trial (SAS)

System Organ Class Preferred Term	SYD985 N=288 n (%)	Physician's Choice N=137 n (%)
Patients with at least 1 grade ≥3 TEAE	152 (52.8)	66 (48.2)
Eye disorders	61 (21.2)	0
Conjunctivitis	16 (5.6)	0
Keratitis	35 (12.2)	0
Dry eye	12 (4.2)	0
General disorders and administration site conditions	18 (6.3)	4 (2.9)
Fatigue	9 (3.1)	2 (1.5)
Gastrointestinal disorders	12 (4.2)	6 (4.4)
Diarrhoea	3 (1.0)	3 (2.2)
Skin and subcutaneous tissue disorders	5 (1.7)	6 (4.4)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	5 (3.6)
Respiratory, thoracic and mediastinal disorders	20 (6.9)	8 (5.8)
Pneumonitis	6 (2.1)	0
Infections and infestations	15 (5.2)	4 (2.9)
Nervous system disorders	5 (1.7)	6 (4.4)
Neuropathy peripheral	2 (0.7)	3 (2.2)
Investigations	28 (9.7)	16 (11.7)
Neutrophil count decreased	5 (1.7)	9 (6.6)
White blood cell count decreased	5 (1.7)	4 (2.9)
Metabolism and nutrition disorders	8 (2.8)	3 (2.2)
Hypokalaemia	2 (0.7)	3 (2.2)
Blood and lymphatic system disorders	25 (8.7)	30 (21.9)
Anaemia	7 (2.4)	1 (0.7)
Neutropenia	14 (4.9)	25 (18.2)
Cardiac disorders	6 (2.1)	1 (0.7)

Abbreviations: AE, adverse event; E, number of treatment-emergent adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Note: AEs were coded by using MedDRA version 23.1.
Note: TEAEs were AEs reported to start within the in-treatment period. The in-treatment period was defined as the period starting from the first dosing of study drug up to and including the treatment discontinuation visit.
Note: Patients who experienced the same coded event more than once were counted only once for the coded event with the highest grade. The highest grade the patient experienced was counted for the overall summaries. The total rows are the total number of patients for the system organ class or preferred term.

Adverse events of special interest (AESI)

AESIs were defined in the protocol to assure that previously observed safety signals with SYD985 treatment (ocular toxicity and ILD/pneumonitis) and/or general safety signals for HER2-targeting drugs (LVEF decrease) would be reported expeditiously and additional details would be available on these AEs and their resolution. The following events were determined as AESI:

- Interstitial lung disease (ILD)/Pneumonitis of any grade
- Severe ocular toxicity grade ≥ 3

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

Treatment-emergent AESIs were reported in 34.7% of patients in the SYD985 group; of these, 27.8% of patients had ocular toxicity, 7.6% had interstitial lung disease, pneumonitis, or lung opacity, and 3.1% had ejection fraction decreased. Only 1 AESI (i.e., ejection fraction decreased) was reported in the physician's choice group, which was expected as the AESIs were specifically defined for SYD985 treatment.

- *Ocular toxicity*

The ocular toxicity is the main toxicity associated to SYD985 with a high incidence of eye disorders. In the TULIP study, there is a large imbalance of the reported TEAEs in the SOC Eye disorders between the SYD985 and the Physician's choice arms, i.e. **78.1% vs 29.2%,** respectively. While the ocular toxicity is a known toxicity of ADCs, it is emphasised that only dry eyes is considered as ADR in the other conjugated trastuzumab (i.e. trastuzumab deruxtecan, trastuzumab emtansine). Ocular toxicity including severe ocular toxicity and Grade ≥2 keratitis can therefore be considered as an emerging risk with SYD985.

Extensive and regular ophthalmological examinations were introduced during the phase I trial and included in all subsequent clinical trials. The proposed monitoring of the ocular toxicity in the SmPC was strengthened compared to TULIP study and includes more examinations to be conducted prior to every infusion while the study flowchart planned an examination every 2 cycles from Cycle 2.

In all trials patients in the SYD985 group prophylactic lubricating eye drops were prescribed and all patients were advised not to wear contact lenses during SYD985 treatment. Specific dose modification instructions for ocular toxicity were included in the clinical trial protocols. Patients who experienced grade ≥3 keratitis had to be discontinued from treatment in the pivotal phase III trial. For patients who developed grade 3 conjunctivitis, dosing had to be delayed and treatment could be continued when toxicity resolved to grade 2 or lower.

In the SYD85.002 trial, most patients had a maximum severity of grade 1 ocular events (27.8% of all patients in the SYD985 group) or grade 2 ocular events (29.2%); grade 3 ocular events were reported in 20.5% of patients in the SYD985 group, and 2 patients (0.7%) had a grade 4 ocular event. Ocular TEAEs of grade 3 or higher that were reported for more than 2% of patients in the SYD985 group were keratitis (12.2%), conjunctivitis (5.6%), and dry eye (4.2%).

Ocular toxicity resulted in discontinuation of treatment in 20.8% of the patients and to dose modification in 22.9% of patients in the SYD985 group, with keratitis, conjunctivitis and dry eye as most common reasons. The proportion of ocular toxicity occurring with SYD985 that improved or resolved was higher for the Grade 3 events compared to the Grade 2 in study SYD985.002, i.e. 64% and 42%, respectively. While conjunctivitis had the highest rate of improvement or resolution among the ocular events (70% for Grade 2 and 100% for Grade 3 events), it is noted that dry eyes only improved/resolved in 38% of the Grade 2 and 50% of the Grade 3 events based on the table below.

Tables 67-69 summarise the action taken with dose delay and dose reduced separately.

Table 67: Number of grade 2 and 3 events of Dry eye by action taken and outcome (OS databaselock)

AE term	Grade	Action taken with IMP	TEAE outcome	N	(%)
Dry eye	**3**	**Total number**		**12**	**100%**
		None	**Total number**	**1**	**100%**
			Resolved/recovered	0	0%
			Before disc. of treatment	0	0%
			After disc. of treatment	0	0%
			Not resolved/not recovered	1	100%
		Dose delay	**Total number**	**2**	**100%**
			Resolved/recovered	1	50%
			Before disc. of treatment	1	50%
			After disc. of treatment	0	0%
			Not resolved/not recovered	1	50%
		Dose reduction	**Total number**	**2**	**100%**
			Resolved/recovered	2	100%
			Before disc. of treatment	1	50%
			After disc. of treatment	1	50%
			Not resolved/not recovered	0	0%
		Disc. of treatment	**Total number**	**7**	**100%**
			Resolved/recovered	5	71%
			Before disc. of treatment	0	0%
			After disc. of treatment	5	71%
			Not resolved/not recovered	2	29%
	2	**Total number**		**27**	**100%**
		None	**Total number**	**21**	**100%**
			Resolved/recovered	10	48%
			Before disc. of treatment	6	29%
			After disc. of treatment	4	19%
			Not resolved/not recovered	11	52%
		Dose delay	**Total number**	**2**	**100%**
			Resolved/recovered	2	100%
			Before disc. of treatment	2	100%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Dose reduction	**Total number**	**4**	**100%**
			Resolved/recovered	3	75%
			Before disc. of treatment	2	50%
			After disc. of treatment	1	25%
			Not resolved/not recovered	1	25%
		Disc. of treatment	**Total number**	**0**	**100%**
			Resolved/recovered	0	0%
			Before disc. of treatment	0	0%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%

Table 68: Number of grade 2 and 3 events of conjunctivitis by action taken and outcome (OS databaselock)

AE term	Grade	Action taken with IMP	TEAE outcome	N	(%)
Conjunctivitis	**3**	**Total number**		**18**	**100%**
		None	**Total number**	**1**	**100%**
			Resolved/recovered	1	100%
			Before disc. of treatment	1	100%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Dose delay	**Total number**	**7**	**100%**
			Resolved/recovered	7	100%
			Before disc. of treatment	7	100%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Dose reduction	**Total number**	**0**	**100%**
			Resolved/recovered	0	0%
			Before disc. of treatment	0	0%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Disc. of treatment	**Total number**	**10**	**100%**
			Resolved/recovered	9	90%
			Before disc. of treatment	1	10%
			After disc. of treatment	8	80%
			Not resolved/not recovered	1	10%
	2	**Total number**		**82**	**100%**
		None	**Total number**	**48**	**100%**
			Resolved/recovered	38	79%
			Before disc. of treatment	34	71%
			After disc. of treatment	4	8%
			Not resolved/not recovered	10	21%
		Dose delay	**Total number**	**15**	**100%**
			Resolved/recovered	14	93%
			Before disc. of treatment	14	93%
			After disc. of treatment	0	0%
			Not resolved/not recovered	1	7%
		Dose reduction	**Total number**	**10**	**100%**
			Resolved/recovered	10	100%
			Before disc. of treatment	10	100%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Disc. of treatment	**Total number**	**9**	**100%**
			Resolved/recovered	6	67%
			Before disc. of treatment	1	11%
			After disc. of treatment	5	56%
			Not resolved/not recovered	3	33%

Table 69: Number of grade 2 and 3 events of keratitis by action taken and ouctome (OS databaselock)

AE term	Grade	Action taken with IMP	TEAE outcome	N	(%)
Keratitis	**3**	**Total number**		**34**	**100%**
		None	**Total number**	**1**	**100%**
			Resolved/recovered	1	100%
			Before disc. of treatment	0	0%
			After disc. of treatment	1	100%
			Not resolved/not recovered	0	0%
		Dose delay	**Total number**	**0**	**100%**
			Resolved/recovered	0	0%
			Before disc. of treatment	0	0%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Dose reduction	**Total number**	**0**	**100%**
			Resolved/recovered	0	0%
			Before disc. of treatment	0	0%
			After disc. of treatment	0	0%
			Not resolved/not recovered	0	0%
		Disc. of treatment	**Total number**	**33**	**100%**
			Resolved/recovered	26	79%
			Before disc. of treatment	5	15%
			After disc. of treatment	21	64%
			Not resolved/not recovered	7	21%
	2	**Total number**		**67**	**100%**
		None	**Total number**	**35**	**100%**
			Resolved/recovered	26	74%
			Before disc. of treatment	18	51%
			After disc. of treatment	8	23%
			Not resolved/not recovered	9	26%
		Dose delay	**Total number**	**14**	**100%**
			Resolved/recovered	13	93%
			Before disc. of treatment	11	79%
			After disc. of treatment	2	14%
			Not resolved/not recovered	1	7%
		Dose reduction	**Total number**	**8**	**100%**
			Resolved/recovered	8	100%
			Before disc. of treatment	5	63%
			After disc. of treatment	3	38%
			Not resolved/not recovered	0	0%
		Disc. of treatment	**Total number**	**10**	**100%**
			Resolved/recovered	3	30%
			Before disc. of treatment	0	0%
			After disc. of treatment	3	30%
			Not resolved/not recovered	7	70%

The median time to onset of first ocular adverse event was 1.2 months, with increasing severity over time. The same trend was reported in the KM analysis. Grade ≥1 dry eye was generally the first event to be reported.

Incidence and resolution of grade 2 and grade 3 ocular toxicity overall and for the 3 most commonly reported ocular TEAEs is summarised in Table 70 (CSR V1.0, 06 October 2021) and Table (CSR V1.0, 20 March 2023).

Table 52: Incidence and resolution of Grade 2 and Grade 3 ocular toxicity in SYD985 treated patients in SYD985.002 trial (SAS) - CSR V1.0, 06 October 2021

	Maximum severity Grade 2		Maximum severity Grade 3	
	All N	Improved or Resolved n (%)	All n	Improved or Resolved n (%)
Patients with at least 1 ocular event*	84	35 (42)	59	38 (64)
Most commonly reported preferred terms				
Dry eye	16	6 (38)	12	6 (50)
Conjunctivitis	50	35 (70)	16	16 (100)
Keratitis	37	16 (43)	34	21 (62)

Numbers indicate the number of patients with worst grade ocular event(s). Number of patients with improved or resolved events includes patients with events that fully resolved or improved to a lower severity grade. The percentage is calculated with the number of patients in each category as denominator.
*includes all TEAEs in the SOC Eye disorders and conjunctivitis

Table 71: Incidence and Resolution of Conjunctivitis, Keratitis, and Dry Eye – SAS(SYD985) - CSR V1.0, 20 March 2023

		Conjunctivitis	Keratitis	Dry Eye
Number of events	n	218	208	117
Grade 1	n	117	98	77
Grade 2	n	83	72	27
Grade ≥3	n	18	38	13
Number of resolved events [1]	n	165	153	52
Grade 1	n	80	68	29
Grade 2	n	68	54	15
Grade 3	n	17	30	8
Grade 4	n	0	1	0

Abbreviations: n, number of events; SAS, safety analysis set.
[1] End date was present.
Cross-reference: Listing 16.2.7.5.1 to Listing 16.2.7.5.3
Source: Table 14.3.3.5.1.1, Table 14.3.3.5.2.1, Table 14.3.3.5.3.1

The applicant stated that recovery of ocular toxicity is observed, but may take weeks to months in particular for higher grade events; a table summarizing the duration of the ocular disorders by PT and severity grade for subjects treated with SYD985 and data on the time to resolution specified for the most frequent grade 2 and grade ≥ 3 ocular toxicities. i.e. keratitis, conjunctivitis, dry eye was provided.

Table 72: Duration of most prevalent ocular toxicity (conjunctivitis, keratitis and dry eye) in SYD985 treated patients per highest severity grade in trial SYD985.002 (SAS) (OS DBL 30 June 2022)

Conjunctivitis (worst grade)	All patients n / total N patients (%)	Recovered/Resolved[2] n/N patients per grade (%)	Duration to resolution in days [1] median, (range)
Grade 1	44/288 (15)	23/44 (52)	43, (8-270)
Grade 2	50/288 (17)	36/50 (72)	26, (6-920)
Grade 3	16/288 (6)	15/16 (94)	27, (11-344)
Keratitis (worst grade)	**All patients n / total N patients (%)**	**Recovered/Resolved [2] n /N patients per grade (%)**	**Duration to resolution in days [1] median, (range)**
Grade 1	38/288 (13)	15/38 (40)	57, (14-206)
Grade 2	36/288 (13)	22/36 (43)	81, (6-828)
Grade 3	35/288 (12)	28/35 (80)	58, (7-725)
Grade 4	1/288 (0.3)	1/1 (100)	22
Dry eye (worst grade)	**All patients n / total N patients (%)**	**Recovered/Resolved [2] n /N patients per grade (%)**	**Duration to resolution in days [1] median, (range)**
Grade 1	59/288 (20)	13/59 (22)	62, (7-596)
Grade 2	16/288 (6)	6/16 (38)	69, (30-205)
Grade 3	12/288 (4)	7/12 (58)	221, (7-697)

[1] Duration calculated as: Highest grade onset (AE start date) to resolution (AE stop date).
[2] Includes Recovered/Resolved and Recovered/Resolved with sequelae.

Table 73: Summary of most common grade ≥2 ocular Aes (conjunctivitis, keratitis and dry eye) fully resolved and incompletely resolved in SYD985 treated patients in trial SYD985.002 (SAS) (OS DBL 30 June 2022)

Conjunctivitis (worst grade)	Fully recovered/resolved n / N patients per grade (%)	Duration in days [1] median (range)	Incompletely resolved (resolving/not resolved at end of follow-up) n / N patients per grade (%)	Grade at end follow-up Grade 3 (n,%)	Grade 2 (n,%)	Grade 1 (n,%)	Duration in days [2] median (range)
Grade 2	24/50 (48)	57, (6-980)	26/50 (52)	-	13 (26)	13 (26)	560, (29-1217)
Grade 3	11/16 (69)	97, (11-344)	5/16 (31)	1 (6)	1 (6)	3 (19)	478, (220-1192)
Keratitis (worst grade)	**Fully recovered/resolved n / N patients per grade (%)**	**Duration in days [1] median (range)**	**Incompletely resolved (resolving/not resolved at end of follow-up) n / N patients per grade (%)**	**Grade at end follow-up Grade 3 (n,%)**	**Grade 2 (n,%)**	**Grade 1 (n,%)**	**Duration in days [2] median (range)**
Grade 2	19/36 (53)	93, (8-836)	17/36 (47)	-	13 (36)	4 (11)	490, (26-1222)
Grade 3	24/35 (69)	61, (9-725)	11/35 (31)	7 (20)	1 (3)	3 (9)	637, (352-1193)
Grade 4	0/1 (0)	-	1/1 (100)	-	-	1 (100)	1288 [3]
Dry eye (worst grade)	**Fully recovered/resolved n / N patients per grade (%)**	**Duration in days [1] median (range)**	**Incompletely resolved (resolving/not resolved at end of follow-up) n/ N patients per grade (%)**	**Grade at end follow-up Grade 3 (n,%)**	**Grade 2 (n,%)**	**Grade 1 (n,%)**	**Duration in days [2] median (range)**
Grade 2	5/16 (31)	77, (51-205)	11/16 (69)	-	10 (91)	1 (9)	544, (181-1201)
Grade 3	6/12 (50)	247, (43-697)	6/12 (50)	5 (83)	1 (17)	-	606, (93-1135)

[1] Duration calculated as: Highest grade onset (AE start date) to resolution (AE stop date) at lowest grade.
[2] Duration calculated as: Highest grade onset (AE start date) to end of AE follow-up period (including lower grade AEs).
[3] This grade 4 keratitis event (patient [redacted]) started on Day 117 and (after 22 days) gradually improved to grade 3 (Day 139), improved further (after 23 days) to grade 2 (Day 162) and subsequently (after 81 days) to grade 1 (Day 243). The grade 1 event was ongoing at end of AE follow-up (Day 1404, 1162 days later). (see narrative in Section 14.3.3 of the SYD985.002 trial report).

- *ILD/pneumonitis*

The underlying mechanism of the development of ILD/pneumonitis with SYD985, but also with other HER2-targeting drugs and ADCs, has not been elucidated and possible risk factors are not yet identified.

ILD/pneumonitis (including all terms) was reported in 34 of the 556 patients (6.1%) treated with SYD985 in any of the trials, with grade 3 or 4 events in 7 patients (1.3%). The incidence of ILD/pneumonitis in subjects treated with SYD985 in the TULIP study (8.7%) is greater in comparison to the other trials (2.7% in SYD985.001, 3.8% in SYD985.003 and 6.7% in SYD985.004).

For 11 patients (2.0%), ILD/pneumonitis was reported as serious TEAE. Four cases (0.7%) of ILD/pneumonitis led to death. Two life-threatening events of ILD/pneumonitis were ongoing at the time

of death due to pneumonia (patient in SYD985.002 trial) or due to other reason (patient in SYD985.001 trial). For 21 of the 28 patients (75%) with mild to severe ILD/pneumonitis, the event improved or completely resolved. For the other events (5 mild, 1 moderate, 1 severe), no resolution date was entered in the clinical database. All ILD/pneumonitis events were reported as related to SYD985.

Table 74: Overview of ILD/pneumonitis cases in SYD985 treated patient (SAS)

	SYD985.001 N=185 n (%)	**SYD985.002 N=288 n (%)**	**SYD985.003 N=53 n (%)**	**SYD985.004 N=30 n (%)**	**Total N=556 n (%)**
Patients with at least 1 event of ILD/pneumonitis	5 (2.7)	25 (8.7)	2 (3.8)	2 (6.7)[1]	34 (6.1)
PT reported:					
Pneumonitis	5 (2.7)	19 (6.6)	2 (3.8)	2 (6.7)[1]	28 (5.0)
Interstitial lung disease	0	3 (1.0)	0	0	3 (0.5)
Lung opacity	0	1 (0.3)	0	0	1 (0.2)
Organising pneumonia	0	1 (0.3)	0	0	1 (0.2)
Radiation pneumonitis	0	1 (0.3)	0	0	1 (0.2)

Search included the following preferred terms: pneumonitis, radiation pneumonitis, ILD, pulmonary fibrosis, organising pneumonia, acute respiratory distress syndrome (ARDS), interstitial pneumonia, pleural fibrosis, and lung opacity
[1] This includes a patient with pneumonitis 1 day after the cut-off date of October 8, 2021

Table 75:CTCAE grade and resolution of ILD/pneumonitis cases (worst severity) in SYD985 treated patients (SAS)

	SYD985.001 N=185		**SYD985.002 N=288**		**SYD985.003 N=53**		**SYD985.004 N=30**		**Total N=556**	
	All n (%)	**Resolved n (%)**	**All n (%)**	**Resolved n (%)**	**All n (%)**	**Resolved n (%)**	**All n (%)**	**Resolved n (%)**	**All n (%)**	**Resolved n (%)**
Grade 1	1 (0.5)	1 (100)	6 (2.1)	3 (50)	2 (3.8)	0	0	0	9 (1.6)	4 (44)
Grade 2	2 (1.1)	2 (100)	11 (3.8)	10 (91)	0	0	1 (3.3)	1 (100)	14 (2.5)	13 (93)
Grade 3	0	0	5 (1.7)	4 (80)	0	0	0	0	5 (0.9)	4 (80)
Grade 4	1 (0.5)	0	1 (0.3)	0	0	0	0	0	2 (0.4)	0
Grade 5	1 (0.5)	0	2 (0.7)	0	0	0	1 (3.3)[1]	0	4 (0.7)	0
All grades	**5 (2.7)**	**3 (60)**	**25 (8.7)**	**17 (68)**	**2 (3.8)**	**0**	**2 (6.7)[1]**	**1 (50)**	**34 (6.1)**	**21 (62)**

Search included the following preferred terms: pneumonitis, radiation pneumonitis, ILD, pulmonary fibrosis, organizing pneumonia, acute respiratory distress syndrome (ARDS), interstitial pneumonia, pleural fibrosis, and lung opacity
Cut-off date for trials SYD985.003 and SYD985.004 was October 8, 2021
Note: Numbers indicate the number of patients with a certain worst grade ILD/pneumonitis event. Number of patients with resolved events includes patients with events that fully resolved or improved to a lower severity grade. The percentage is calculated with the number of patients in each category as denominator.
[1] This includes a patient with pneumonitis 1 day after the cut-off date

The time to onset of ILD/pneumonitis was comparable between the different CTCAE grade and seems not to be impacted by the severity of the event, i.e. median TTO of 4.1 months for Grade ≥1, 4.5 months for Grade ≥2 and 3.6 months for Grade ≥3.

The management of the pulmonary toxicity was similar in the phase 3 study and the proposed SmPC: patients who experienced grade ≥2 ILD/pneumonitis (at start of the phase III trial this was grade ≥3) had to be discontinued from treatment and for patients with grade 1 ILD/pneumonitis, dosing had to be delayed. The applicant introduced of a dose reduction while resuming treatment, similarly to Grade 1 ILD/pneumonitis that resolved greater than 28 days for trastuzumab deruxtecan. The Grade 2-3 cases of ILD/pneumonitis were manageable most of the time taking into account that the Grade 2 cases were the most common reported events. Nevertheless, the seriousness of the pulmonary toxicity is of concern considering the fatal cases occurring in SYD985-treated subjects.

- *Left Ventricular Dysfunction (LVD)*

Cardiac toxicity is a known risk of HER2-targeting drugs including congestive heart failure for trastuzumab and left ventricular dysfunction for the conjugated trastuzumab.

Ejection fraction decreased was reported as TEAE in 26 of 556 patients (4.7%) treated with SYD985 in any of the trials, with grade ≥3 events in 7 patients (1.3%). In the pivotal phase III trial, 11 patients (3.8%) in the SYD985 group reported ejection fraction decreased, with a grade 3 event in 2 patients (0.7%) and a grade 4 event in 1 patient (0.3%).

Table 53: Overview of TEAE ejection fraction decreased in patients treated with SYD985 (SAS)

Trial number:	**SYD985.001 N=185 n (%)**	**SYD985.002 N=288 n (%)**	**SYD985.003 N=53 n (%)**	**SYD985.004 N=30 n (%)**	**Total N=556 n (%)**
Patients with at least 1 event of ejection fraction decreased	13 (7.0)	11 (3.8)	1 (1.9)	1 (3.3)	26 (4.7)
Worst case CTCAE grade reported					
Grade 1 – mild	4 (2.2)	1 (0.3)	0	0	5 (0.9)
Grade 2 – moderate	7 (3.8)	7 (2.4)	0	0	14 (2.5)
Grade 3 - severe	2 (1.1)	2 (0.7)	1 (1.9)	1 (3.3)	6 (1.1)
Grade 4 – life threatening	0	1 (0.3)	0	0	1 (0.2)

- *Infusion related reactions*

Infusion related reactions (IRRs) were reported in 38 of 556 patients (6.8%) treated with SYD985 in any of the trials, with grade 3 events in 3 patients (0.5%). No grade 4 IRR events occurred. All IRRs occurred at the start of SYD985 treatment, either after the first and/or second infusion. For a total of 12 patients (2.2%), infusion rate was reduced or interrupted and most IRRs recovered within 1 day, either with or without any medication given. Based on the data provided, it is supported not to consider the risk of IRR as a safety concern since the great majority of reported IRR were not severe and manageable.

- *Adverse drug reactions*

The applicant provided proposed table for the adverse reactions section of the label, based on the safety data of the phase III SYD985.002 trial. The table includes all TEAEs (including the grouped terms) that were reported in ≥10% of patients and other clinically relevant TEAEs reported in <10% of patients treated with SYD985 in the phase III trial, regardless of relationship to SYD985.

Table 54: Proposed table for label: Adverse reactions in patients treated with SYD985

System organ class	Preferred term or grouped term	Frequency	Reference column (will not appear in label) SYD985.002 N=288 n (%)
Blood and lymphatic system disorders	Neutrophil count decrease[a]	Very common	44 (15.3)
	Anaemia[b]	Very common	41 (14.2)
	Platelet count decrease[c]	Very common	30 (10.4)
Metabolism and nutrition disorders	Decreased appetite	Very common	61 (21.2)
Nervous system disorders	Headache	Very common	33 (11.5)
	Peripheral neuropathy[d]	Common	22 (7.6)
Eye disorders	Keratitis	Very common	110 (38.2)
	Conjunctivitis	Very common	110 (38.2)
	Dry eye	Very common	87 (30.2)
	Corneal disorders[e]	Very common	57 (19.8)
	Lacrimation increased	Very common	53 (18.4)
	Periocular oedema[f]	Very common	39 (13.5)
	Blepharitis	Very common	36 (12.5)
Cardiac disorders	Pericardial effusion	Common	10 (3.5)
Respiratory, thoracic and mediastinal disorders	Cough	Very common	48 (16.7)
	Dyspnoea	Very common	42 (14.6)
	Interstitial lung disease/pneumonitis[g]	Common	25 (8.7)
	Pleural effusion	Common	13 (4.5)
Gastrointestinal disorders	Nausea	Very common	73 (25.3)
	Diarrhoea	Very common	60 (20.8)
	Constipation	Very common	57 (19.8)
	Abdominal pain[h]	Very common	37 (12.8)
	Vomiting	Very common	36 (12.5)
	Stomatitis[i]	Very common	29 (10.1)
Skin and subcutaneous tissue disorders	Alopecia	Very common	62 (21.5)
	Skin hyperpigmentation	Very common	32 (11.1)
Musculoskeletal and connective tissue disorders	Arthralgia	Very common	31 (10.8)
General disorders and administration site conditions	Fatigue	Very common	96 (33.3)
	Asthenia	Very common	58 (20.1)
Investigations	Weight decreased	Very common	29 (10.1)
	Transaminases increased[j]	Common	21 (7.3)
	Ejection fraction decreased	Common	11 (3.8)
Injury, poisoning and procedural complications	Infusion related reaction	Common	12 (4.2)

[a] Includes neutrophil count decreased and neutropenia.
[b] Includes anaemia and haemoglobin decreased.
[c] Includes platelet count decreased and thrombocytopenia.
[d] Includes neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy.
[e] Includes all terms of the Standardized MedDRA Queries (SMQ) group corneal disorders (SMQ, narrow), excluding keratitis.
[f] Includes periorbital oedema, eyelid oedema, eye swelling, periorbital swelling, swelling of eyelid, and eye oedema.
[g] Includes pneumonitis, radiation pneumonitis, interstitial lung disease, pulmonary fibrosis, organising pneumonia, acute respiratory distress syndrome, interstitial pneumonia, pleural fibrosis, and lung opacity.
[h] Includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal discomfort.
[i] Includes stomatitis and mouth ulceration.
[j] Includes transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic enzyme increased, and hepatic function abnormal.

The ADR tachycardia was added upon CHMP request.

3.3.7.3. Serious adverse events, deaths, and other significant events

- *Deaths*

Table 55: Summary of deaths during SYD985 treatment in all clinical trials (SAS)

	SYD985.002		**SYD985.001**			**SYD985.003**	**SYD985.004**
Primary cause of death	**SYD985 N=288 n (%)**	**Physician's Choice N=137 n (%)**	**Total N=185 n (%)**	**Dose escalation Part 1 N=39 n (%)**	**Expansion Part II N=146 n (%)**	**N=53 n (%)**	**N=30 n (%)**
Any cause	9 (3.1)	0	6 (3.2)	3 (7.7)	3 (2.1)	7 (13.2)	1 (3.3)[1]
Disease Progression	3 (1.0)	0	5 (2.7)	2 (5.1)	3 (2.1)	3 (5.7)	0
Related TEAE	4 (1.4)	0	1 (0.5)	1 (2.6)	0	0	0[1]
Unrelated TEAE	2 (0.7)	0	0	0	0	4 (7.5)	0
Unknown	0	0	0	0	0	0	1 (3.3)

Note: included are all deaths up to the treatment discontinuation visit 4 to 6 weeks after the last trial drug administration (SYD985.002) or up to the 30-days FU visit (other trials), and deaths that occurred after this period as an outcome of one or more TEAEs
Note: cut-off date for ongoing trials SYD985.003 and SYD985.004 was October 8, 2021
[1] A fatal event occurred 1 day after the cut-off date

In **Study SYD985.002**, six fatal AEs were reported in 6 patients of the SYD985 group; no fatal AEs were reported in patients of the physician's choice group.

- A patient, who had lung metastases, had pneumonitis that was considered probably related to trial drug; the patient received a total of 7 cycles prior to death. After approximately 3 months, an SAE of pneumonitis of moderate intensity was documented. It was decided to permanently discontinue treatment with study drug due to this event. The patient continued to deteriorate, despite treatment with steroids and antibiotics, and died due to pneumonitis approximately 9 weeks after its onset.
- A patient had pneumonitis that was considered possibly related to trial drug; the patient received a total of 12 cycles prior to death. Approximately 8 weeks after Cycle 12, the patient was hospitalised because of pneumonitis. During hospitalisation, active *Klebsiella* septicaemia was reported, likely secondary to urosepsis. The patient remained ventilator dependent despite high doses of steroids. The decision was made to not further escalate treatment, and the patient's condition continued to deteriorate. The patient died approximately 6 months after pneumonitis onset.
- Fatal pneumonia was reported in 1 patient with lung metastases. Pneumonitis, pneumonia, and acute respiratory failure were reported after the 6th infusion with SYD985. All 3 events were considered to be probably related to study drug. Over the following 9 days, the chest CT-scans showed improvement, but the respiratory status did not improve. The patient died due to pneumonia. The pneumonitis and acute respiratory failure were reported to be ongoing at the time of death.
- A fatal event of respiratory failure was reported in 1 patient, which was considered to be possibly related to trial drug. This concerned a patient with lung metastases who experienced pneumonia (grade 3, unlikely related) after 5 cycles of SYD985. Following administration of Cycle 10, the

patient developed respiratory failure, which was not responsive to steroid treatment and eventually became fatal.

The other 2 fatal events were considered unlikely related to SYD985 treatment. One patient was reported to have acute respiratory failure that started the day after the first infusion. A CT-scan of the chest on the same day showed interstitial lung disease. The patient died due to the event 4 days later. The second patient died due to COVID-19 pneumonia after 10 infusions with SYD985.

In **Study SYD985.001**, a total of 6 patients died while on SYD985 treatment of which 1 due to a fatal TEAE.

Fatal pneumonitis was reported for a 47-year old female patient with HER2 positive breast cancer diagnosed 3 years before study enrolment. The patient was enrolled in the 2.4 mg/kg SYD985 cohort of the dose escalation Part 1 of the trial. The patient experienced worsening of dyspnoea during treatment cycle 2 which required hospitalisation for antibiotic treatment. The patient appeared to slightly improve and antibiotic treatment was continued up to 10 days. Following the third SYD985 infusion, the symptoms worsened and the patient was readmitted to the hospital 8 days after the third infusion. The patient was diagnosed with grade 3 drug-induced pneumonitis with extensive parenchymal lung changes. Despite oxygen support and high dose corticosteroids treatment, the patient died of respiratory failure approximately 1 month after initial symptoms.

Partly due to this fatality, which was reported as a dose-limiting toxicity, it was decided not to further enrol any patients on this or higher doses, but to evaluate lower SYD985 doses (i.e. 1.8 and 1.5 mg/kg) in more detail.

In the ongoing **Study SYD985.003**, up to the cut-off date, in total 7 patients with endometrial cancer died while on SYD985 treatment. Four patients died due to a TEAE. All events were considered not related to treatment.

In the ongoing **Study SYD985.004**, up to the data cut-off date, one patient died while on SYD985 treatment due to an unknown cause. In addition, 1 day after the cut-off date a patient died due to a TEAE.

A fatal case of pneumonitis was reported for a patient with metastatic breast cancer. The patient experienced respiratory tract infection with shortness of breath and oxygen saturation decreasing to 83% after 6 SYD985 80 mg Powder for Concentrate for Solution for Infusion SYD985 administrations with 0.9 mg/kg SYD985 in combination with 200 mg niraparib once daily. Chest X-ray showed patchy consolidation consistent of infection. COVID-19 infection was excluded. The patient's condition did however not improve with antibiotic treatment and the patient developed worsening of dyspnoea and further deterioration of health. Pneumonitis and pulmonary oedema were considered. Despite extensive treatment, including with antibiotics and corticosteroids, the event did not significantly improve and the patient died of pneumonitis approximately 3.5 weeks after first event. The event of pneumonitis was considered related to SYD985 and to niraparib.

- *Other serious AEs*

Table 56: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (>1 Patient in Any Treatment Group) – Study SYD985.002 (SAS)

System Organ Class Preferred Term	SYD985 N=288 n (%) E		Physician's Choice N=137 n (%) E	
	All	Related	All	Related
Patients with at least 1 serious TEAE	53 (18.4) 93	25 (8.7) 37	12 (8.8) 15	6 (4.4) 8
Respiratory, thoracic and mediastinal disorders	**15 (5.2) 18**	**10 (3.5) 12**	**4 (2.9) 4**	**0**
Pneumonitis	7 (2.4) 8	7 (2.4) 8	0	0
Acute respiratory failure	2 (0.7) 2	1 (0.3) 1	0	0
Pulmonary embolism	1 (0.3) 1	0	1 (0.7) 1	0
Pneumothorax	0	0	3 (2.2) 3	0
Infections and infestations	**14 (4.9) 19**	**3 (1.0) 5**	**3 (2.2) 5**	**2 (1.5) 4**
Pneumonia	3 (1.0) 5	0	1 (0.7) 1	0
Upper respiratory tract infection	1 (0.3) 1	0	1 (0.7) 1	0
Wound infection	2 (0.7) 2	0	0	0
Gastrointestinal disorders	**7 (2.4) 10**	**3 (1.0) 3**	**2 (1.5) 2**	**1 (0.7) 1**
Abdominal pain	2 (0.7) 2	2 (0.7) 2	0	0
Nausea	2 (0.7) 2	1 (0.3) 1	0	0
Diarrhoea	1 (0.3) 1	0	1 (0.7) 1	1 (0.7) 1
Cardiac disorders	**5 (1.7) 5**	**1 (0.3) 1**	**0**	**0**
Investigations	**4 (1.4) 5**	**3 (1.0) 4**	**0**	**0**
Platelet count decreased	2 (0.7) 3	2 (0.7) 3	0	0
Blood and lymphatic system disorders	**3 (1.0) 7**	**1 (0.3) 2**	**1 (0.7) 1**	**1 (0.7) 1**
Anaemia	2 (0.7) 5	0	0	0
General disorders and administration site conditions	**3 (1.0) 3**	**0**	**2 (1.5) 2**	**2 (1.5) 2**
Pyrexia	1 (0.3) 1	0	1 (0.7) 1	1 (0.7) 1
Injury, poisoning and procedural complications	**3 (1.0) 4**	**2 (0.7) 3**	**0**	**0**
Infusion related reaction	2 (0.7) 3	2 (0.7) 3	0	0
Metabolism and nutrition disorders	**3 (1.0) 3**	**0**	**0**	**0**
Hypercalcaemia	2 (0.7) 2	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.0) 5**	0	**0**	0
Eye disorders	**2 (0.7) 5**	**2 (0.7) 5**	**0**	**0**
Keratitis	2 (0.7) 3	2 (0.7) 3	0	0

Abbreviations: AE, adverse event; E, number of treatment-emergent adverse events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Note: AEs were coded by using MedDRA version 23.1.
Note: TEAEs were AEs reported to start within the in-treatment period. The in-treatment period was defined as the period starting from the first dosing of study drug up to and including the treatment discontinuation visit.
Cross-reference: Listing 16.2.7
Source: Table 14.3.1.4, Table 14.3.1.11

In study SYD985.002 a large imbalance of serious TEAEs was observed across the two treatment arms, i.e. 18.4% vs 8.8% in the SYD985 arm and the Physician's choice arm, respectively.

The most commonly reported serious TEAE by PT were pneumonitis (2.4%), abdominal pain (0.7%), platelet count decreased (0.7%), keratitis (0.7%), and infusion related reaction (0.7%). The majority of the serious TEAEs reported in the SYD985 arm recovered/resolved with or without sequelae.

The serious TEAEs that did not resolved occurred in 9 (3.1%) subjects and are listed below:

- Livedo reticularis
- Platelet count decreased
- Chronic myeloid leukaemia
- Acute respiratory failure (fatal case)
- Breast wound infection

- Infected neoplasm/Necrotic left Breast mass infection
- COVID19 induced pneumonia (fatal case)
- Respiratory Failure
- acute respiratory failure
- Pneumonitis
- Pneumonia (fatal case)
- Pneumonitis (fatal case)

3.3.7.4. Laboratory findings

Haematology

Table 80: CTCAE grading of worst case post-baseline haematological parameters for patients with worsening post-baseline values in SYD985.002 trial (SAS)

Hematological parameter	Worst CTCAE grade post-baseline (for patients with worsening post-baseline values)			
	SYD985		Physician's Choice	
	All grades n (%)[1]	Grade 3 or 4 n (%)[1]	All grades n (%)[1]	Grade 3 or 4 n (%)[1]
Haemoglobin high	0	0	1 (0.7)	0
Haemoglobin low	120 (42.1)	8 (2.8)	78 (57.8)	1 (0.7)
Leukocytes high	0	0	0	0
Leukocytes low	158 (55.6)	23 (8.1)	84 (62.2)	30 (22.2)
Lymphocytes high	1 (0.4)	0	2 (1.5)	0
Lymphocytes low	195 (68.9)	37 (13.1)	62 (46.6)	8 (6.0)
Neutrophils	63 (22.3)	18 (6.4)	61 (45.9)	38 (28.6)
Platelets	58 (20.4)	6 (2.1)	29 (21.5)	1 (0.7)

[1] Percentages are calculated with the number of patients in the parameter group with both baseline and post-baseline measurements as denominator

Overall, a worsening of haematological laboratory parameters from baseline was observed in subjects treated by SYD985 (68.9% for low lymphocytes, 55.6% for low leukocytes, 42.1% for low haemoglobin, 22.3% for neutrophils and 20.4% for platelets, all grade) but the worst post-baseline was generally Grade 1-2 and the worsening was less pronounced than in the Physician's choice except for the lymphocytes low.

Blood chemistry

Table 57: CTCAE grading of worst case post-baseline blood chemistry parameters for patients with worsening post-baseline values in SYD985.002 trial (SAS)

Blood chemistry parameter	Worst CTCAE grade post-baseline (for patients with worsening post-baseline values)			
	SYD985		Physician's Choice	
	All grades n (%)[1]	Grade 3 or 4 n (%)[1]	All grades n (%)[1]	Grade 3 or 4 n (%)[1]
ALT	44 (15.3)	2 (0.7)	45 (33.3)	1 (0.7)
Albumin	18 (6.3)	1 (0.3)	7 (5.2)	0
Alkaline phosphatase	53 (18.5)	9 (3.1)	31 (23.0)	1 (0.7)
AST	54 (18.8)	7 (2.4)	38 (28.1)	2 (1.5)
Bilirubin	7 (2.4)	0	13 (9.6)	2 (1.5)
Calcium high	8 (2.8)	1 (0.3)	5 (3.7)	0
Calcium low	72 (25.1)	7 (2.4)	28 (20.7)	3 (2.2)
Creatinine	29 (10.1)	0	13 (9.6)	0
GGT	52 (18.1)	16 (5.6)	35 (25.9)	5 (3.7)
Glucose high	76 (26.7)	8 (2.8)	38 (28.1)	6 (4.4)
Glucose low	46 (16.1)	3 (1.1)	11 (8.1)	0
Magnesium high	11 (3.8)	0	9 (6.7)	0

Blood chemistry parameter	Worst CTCAE grade post-baseline (for patients with worsening post-baseline values)			
	SYD985		Physician's Choice	
	All grades n (%)[1]	Grade 3 or 4 n (%)[1]	All grades n (%)[1]	Grade 3 or 4 n (%)[1]
Magnesium low	70 (24.4)	1 (0.3)	27 (20.0)	0
Potassium high	21 (7.3)	4 (1.4)	3 (2.2)	1 (0.7)
Potassium low	32 (11.1)	6 (2.1)	19 (14.1)	5 (3.7)
Sodium high	7 (2.4)	1 (0.3)	3 (2.2)	0
Sodium low	31 (10.8)	4 (1.4)	16 (11.9)	2 (1.5)

[1] Percentages are calculated with the number of patients in the parameter group with both baseline and post-baseline measurements as denominator

The percentage of patients with worsening post-baseline values was similar or slightly lower in the SYD985 group as compared to the physician's choice group. In addition, the number of patients with worst case grade ≥3 value for any of the parameters was low in both groups.

3.3.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.7.6. Safety in special populations

Age

There was no consistent impact of age on the occurrence of the overall safety endpoints, except for a slight decrease in grade ≥3 TEAEs with increasing age (54% in patients <65 years, 50% for 65-74 years, and 44% in patients ≥75 years). For the individually assessed TEAEs, dry eye was less common in patients between 65 and 74 years (20%) as compared to younger patients (33%). In contrast, decreased appetite was more frequently observed in elderly patients (19% in patients <65 years, 26% for 65-74 years and 38% in patients ≥75 years). For the other TEAEs no relevant difference was observed for age.

Race

Patients of other race seemed to report more serious TEAEs (32%) and more TEAEs leading to dose modifications (62%) than patients of White race (18% and 45%, respectively). However, the numbers should be interpreted with caution as only 34 of the 288 patients (12%) treated with SYD985 were of other race. The other overall endpoints were similar between the subgroups. No consistent pattern was observed for the individual TEAEs in relation to race. Keratitis, dry eye, ejection fraction decreased and ILD/pneumonitis were more commonly reported for patients of other race, whereas lacrimation increased and blepharitis were more common in patients of White race. For 52 patients (18%), race was not disclosed due to national privacy regulations.

Ethnicity

Conclusions on the impact of ethnicity on the safety endpoints could not be drawn as only 11 patients were of Hispanic or Latino ethnicity.

Region

Patients from North America seemed to report more TEAEs of grade ≥3 (64%) as compared to patients from Europe or Asia (50%). Percentages for serious TEAEs and TEAEs leading to drug withdrawal were somewhat higher in North America (24% and 44%, respectively) as compared to Europe (17% and 33%, respectively); the percentages for Asia were comparable to North America. Keratitis and conjunctivitis were reported in clearly higher incidences in Europe and Asia as compared to North America, whereas other TEAEs (i.e. for dry eye, lacrimation increased, decreased appetite, skin hyperpigmentation) were reported more frequently in North America.

Renal function

Table 82: Overall TEAEs by renal impairment for SYD985 treated patients in the SYD985.002 trial (SAS)

	Renal impairment				
	Normal N=166	Mild N=109	Moderate N=12	Unknown N=1	Total N=288
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
TEAEs	158 (95.2)	108 (99.1)	11 (91.7)	1 (100)	278 (96.5)
Serious TEAEs	33 (19.9)	18 (16.5)	1 (8.3)	1 (100)	53 (18.4)
TEAEs leading to treatment discontinuation	55 (33.1)	41 (37.6)	6 (50.0)	0	102 (35.4)
TEAEs leading to dose modifications	68 (41.0)	56 (51.4)	8 (66.7)	0	132 (45.8)
TEAEs of grade ≥3	86 (51.8)	59 (54.1)	6 (50.0)	1 (100)	152 (52.8)
AESIs	52 (31.3)	43 (39.4)	5 (41.7)	0	100 (34.7)

Renal function was classified based on eGFR: Normal: ≥90 mL/min/1.73 m^2; Mild: 60 to <90 mL/min/1.73 m^2; Moderate: 30 to <60 mL/min/1.73 m^2; Severe: 15 to <30 mL/min/1.73 m^2

Table 83: Individual TEAEs by renal impairment for SYD985 treated patients in the SYD985.002 trial (SAS)

	Renal impairment				
	Normal N=166	Mild N=109	Moderate N=12	Unknown N=1	Total N=288
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Conjunctivitis	61 (36.7)	41 (37.6)	8 (66.7)	0	110 (38.2)
Keratitis	59 (35.5)	45 (41.3)	6 (50.0)	0	110 (38.2)
Dry eye	44 (26.5)	39 (35.8)	4 (33.3)	0	87 (30.2)
Lacrimation increased	24 (14.5)	26 (23.9)	3 (25.0)	0	53 (18.4)
Blepharitis	20 (12.0)	15 (13.8)	1 (8.3)	0	36 (12.5)
ILD/Pneumonitis	14 (8.4)	9 (8.3)	1 (8.3)	0	24 (8.3)
Ejection fraction decreased	7 (4.2)	4 (3.7)	0	0	11 (3.8)
Decreased appetite	30 (18.1)	27 (24.8)	4 (33.3)	0	61 (21.2)
Skin hyperpigmentation	16 (9.6)	13 (11.9)	3 (25.0)	0	32 (11.1)

Renal function was classified based on eGFR: Normal: ≥90 mL/min/1.73 m^2; Mild: 60 to <90 mL/min/1.73 m^2; Moderate: 30 to <60 mL/min/1.73 m^2; Severe: 15 to <30 mL/min/1.73 m^2

In SYD985.002 study, the SYD985 treated patient with mild (n=109) and moderate (n=12) renal impairment experienced more keratitis, dry eye and lacrimation increased than subjects with normal renal function (n=166). In addition, more conjunctivitis cases were reported in moderate renal impaired subjects than subjects with normal renal function.

Hepatic function

Table 84: Individual TEAEs by hepatic impairment for SYD985 treated patients in the SYD985.002 trial (SAS)

	Hepatic impairment				
	Normal N=198	Mild N=87	Moderate N=2	Unknown N=1	Total N=288
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Conjunctivitis	79 (39.9)	30 (34.5)	1 (50.0)	0	110 (38.2)
Keratitis	82 (41.4)	28 (32.2)	0	0	110 (38.2)
Dry eye	64 (32.3)	23 (26.4)	0	0	87 (30.2)
Lacrimation increased	39 (19.7)	14 (16.1)	0	0	53 (18.4)
Blepharitis	24 (12.1)	12 (13.8)	0	0	36 (12.5)
ILD/Pneumonitis	18 (9.1)	6 (6.9)	0	0	24 (8.3)
Ejection fraction decreased	8 (4.0)	3 (3.4)	0	0	11 (3.8)
Decreased appetite	42 (21.2)	19 (21.8)	0	0	61 (21.2)
Skin hyperpigmentation	23 (11.6)	9 (10.3)	0	0	32 (11.1)

Hepatic function was classified according to the NCI-ODWG criteria (Patel et al., 2004): Normal: bilirubin and AST ≤ ULN; Mild: (bilirubin > ULN to 1.5× ULN) or (bilirubin ≤ULN and AST >ULN); Moderate: bilirubin >1.5× to 3× ULN, any AST; Severe: bilirubin >3× ULN, any AST

Serious AEs were more reported in subjects treated with SYD985 in the pivotal study with mild hepatic impairment compared to subjects with normal hepatic function (i.e. 25.3% and 14.6%, respectively). No impact of the hepatic function was observed on individual TEAE.

MedDRA Terms	Age <65 N=222 n (%)	Age 65-74 N=50 n (%)	Age 75-84 N=16 n (%)	Age 85+ N=0 n (%)
Total TEAEs	216 (97.3)	47 (94.0)	15 (93.8)	0
Serious TEAEs -Total	42 (18.9)	8 (16.0)	3 (18.8)	0
Fatal[4]	4 (1.8)	1 (2.0)	1 (6.3)	0
Hospitalization/prolong existing hospitalization[4]	40 (18.0)	6 (12.0)	5 (31.3)	0
Life-threatening[4]	5 (2.3)	0	1 (6.3)	0
Disability/incapacity[4]	0	1 (2.0)	0	0
Other (medically significant) [4]	5 (2.3)	0	0	0
TEAEs leading to treatment discontinuation	78 (35.1)	19 (38.0)	5 (31.3)	0
Psychiatric disorders (SOC)	37 (16.7)	5 (10.0)	1 (6.3)	0
Nervous system disorders (SOC)	78 (35.1)	16 (32.0)	5 (31.3)	0
Accidents and injuries[1]	12 (5.4)	3 (6.0)	1 (6.3)	0
Cardiac disorders (SOC)	20 (9.0)	7 (14.0)	2 (12.5)	0
Vascular disorders (SOC)	22 (9.9)	8 (16.0)	3 (18.8)	0
Cerebrovascular disorders (PT)	0	0	0	0
Infections and infestations (SOC)	130 (58.6)	36 (72.0)	7 (43.8)	0
Anticholinergic syndrome (PT)[2]	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension[3], falls, black outs[2], syncope, dizziness, ataxia, fractures (PTs)	17 (7.7)	6 (12.0)	1 (6.3)	0

[1] SMQ 'Accidents and injuries' narrow
[2] SMQ 'anticholinergic syndrome' narrow
[3] Includes PTs 'orthostatic hypotension' for postural hypotension and 'loss of consciousness' for black outs
[4] Information on SAE criterion/reason was obtained from the safety database

Use in pregnancy and breastfeeding

Concerning the use in pregnant women, according to human data on trastuzumab, it is expected that a teratogenic and fetotoxic risk will be observed in case of exposure during pregnancy. Therefore, Jivadco should not be used during pregnancy. It is noted that a period of contraception after discontinuation treatment should be used considering the mutagenic effect of SYD986. The $t_{1/2}$ of SYD986 is 6 days. Therefore, a contraception period of 7 months in women of childbearing potential and 4 months in men with female partners of childbearing potential is acceptable.

There is no information concerning the use of Jivadco during breastfeeding. Given the safety profile of SYD985 and SYD986, women are advised not to breastfeed and a time period for resuming breast-feeding 2 months after stopping treatment is recommended.

3.3.7.7. Immunological events

At baseline there were 3 (1.1%) patients in study SYD985.002 and none in study SYD985.001 with a confirmed positive result. The majority of the patients were ADA negative, 260 (93.5%) patients, and only 6 (2.2%) patients were ADA positive. ADAs were detected in 10 (3.6%) patients. The ADA response was treatment induced in 6 (2.2%) patients. The ADA response was transient in 5 (1.8%) patients.

Table 85: overview of the immunogenicity results obtained in two clinical trials with SYD985

Parameter	SYD985.001	SYD985.002
Reference to data	BDR.NL03.83683	CR.NL03.89705
Total # Subjects in ADA set # Samples analyzed # Baseline samples # In-treatment samples	185 (100%) 1332 (Baseline + In-treatment)	– 278 (100%) – 1768 – 226 (81.3%) – 1542 (Depending on visit number between 64.5% and 100% of subjects had ADA samples analyzed)
Subject status • ADA-positive • ADA-negative • ADA-inconclusive • Unevaluable	 0 (0%) 171 (92%) 9 (5%) 5 (3%)	 6 (2.2%) 260 (93.5%) 1 (0.4%) 11 (4.0%)
ADA detected • Yes • No • N/A	No ADA-positive samples/patients were detected.	 10 (3.6%) 266 (95.7%) 2 (0.7%)
Pre-treatment ADA • Yes • No • N/A		 3 (1.1%) 218 (78.4%) 57 (20.5%)
Treatment boosted or induced • Treatment boosted • Treatment induced • N/A		 0 6 (2.2%) 272 (97.8%)
Transient or persistent response • Transient response • Persistent response • N/A		 5 (1.8%) 0 273 (98.2%)
ADA prevalence		3.3%
ADA incidence		0.7%

Patient was the only patient with 4 in-treatment ADA positive samples and the only patient with a measurable titre. For this patient, infusion related reactions (IRR) were reported for treatment cycles 2, 3 and 4. The intravenous infusion with SYD985 was interrupted. Each of the three IRR adverse events (AEs) were reported as recovered/resolved on the same day. The first IRR was of moderate severity. With the two subsequent infusions of SYD985 prophylactic treatment was given. The two subsequent IRRs were of mild severity. Following the last IRR it was decided to discontinue treatment.

IRRs were reported in 12 (4.2%) patients treated with SYD985, patient was the only patient with ADAs detected. Infusion site reaction was reported in 1 (0.3%) patient treated with SYD985, for this patient no ADAs were detected. This supports an acceptable impact of ADA on the safety profile of SYD985.

3.3.7.8. Safety related to drug-drug interactions and other interactions

See PK interactions.

3.3.7.9. Discontinuation due to adverse events

- *TEAEs leading to treatment discontinuation*

Table 58: TEAEs leading to treatment discontinuation (1 or 2 drugs for physician's choice) in ≥1% of patients in any treatment group SYD985.002 trial (SAS)

System Organ Class Preferred Term	**SYD985 N=288 n (%)**		**Physician's Choice N=137 n (%)**	
	All	**Related**	**All**	**Related**
Patients with at least 1 TEAE leading to permanent discontinuation of trial drug	102 (35.4)	95 (33.0)	14 (10.2)	9 (6.6)
Eye disorders	**60 (20.8)**	**60 (20.8)**	**0**	**0**
Keratitis	39 (13.5)	39 (13.5)	0	0
Conjunctivitis	19 (6.6)	19 (6.6)	0	0
Dry eye	7 (2.4)	7 (2.4)	0	0
Eyelid oedema	4 (1.4)	4 (1.4)	0	0
Blepharitis	3 (1.0)	2 (0.7)	0	0
Periorbital oedema	3 (1.0)	3 (1.0)	0	0
Respiratory, thoracic and mediastinal disorders	**18 (6.3)**	**17 (5.9)**	**5 (3.6)**	**0**
Pneumonitis	14 (4.9)	14 (4.9)	0	0
Dyspnoea	0	0	2 (1.5)	0
Investigations	**9 (3.1)**	**8 (2.8)**	**3 (2.2)**	**3 (2.2)**
Neutrophil count decreased	1 (0.3)	1 (0.3)	2 (1.5)	2 (1.5)
Ejection fraction decreased	3 (1.0)	3 (1.0)	0	0
Platelet count decreased	3 (1.0)	3 (1.0)	0	0
General disorders and administration site conditions	**7 (2.4)**	**6 (2.1)**	**3 (2.2)**	**2 (1.5)**
Fatigue	4 (1.4)	4 (1.4)	2 (1.5)	1 (0.7)

Note: AEs were coded using MedDRA version 23.1

In study SYD985.002, the rate of treatment discontinuation due to TEAEs was higher in the SYD985 group compared to the Physician's choice group, i.e. 35.4% vs 10.2% respectively, mainly driven by the eye disorders (20.8% vs 0). The majority of the TEAEs leading to treatment discontinuation is the SYD985 group was treatment-related.

In study SYD985.001, a total of 11 patients (28.2%) in Part I and 29 patients (19.9%) in Part II discontinued treatment due to one or more TEAEs. Almost all TEAEs that led to permanent discontinuation of trial drug were considered to be related to SYD985. In Cohort A of Part II, a total of 7 patients (14.0%) discontinued treatment due to one or more TEAEs. In Part II, The TEAEs leading to discontinuation for more than 2 patients were conjunctivitis (3.4%) and keratitis (2.7%). Percentages observed in cohort A were comparable to the overall percentages observed in all patient cohorts combined.

Overall, the rate of discontinuations due to TEAEs with SYD985 raises concerns on the tolerability of the treatment, especially the ocular toxicity.

- *TEAEs leading to dose modifications*

Table 59: TEAEs leading to dose modifications of trial drug in ≥ 2% of patients in any treatment group SYD985.002 trial (SAS)

System Organ Class Preferred Term	SYD985 N=288 n (%)		Physician's Choice N=137 n (%)	
	All	Related	All	Related
Patients with at least 1 TEAE leading to dose modification of trial drug	132 (45.8)	111 (38.5)	74 (54.0)	68 (49.6)
Eye disorders	**66 (22.9)**	**65 (22.6)**	**0**	**0**
Conjunctivitis	28 (9.7)	27 (9.4)	0	0
Keratitis	22 (7.6)	21 (7.3)	0	0
Dry eye	9 (3.1)	9 (3.1)	0	0
Investigations	**28 (9.7)**	**21 (7.3)**	**13 (9.5)**	**11 (8.0)**
Weight decreased	9 (3.1)	6 (2.1)	0	0
Neutrophil count decreased	6 (2.1)	5 (1.7)	7 (5.1)	7 (5.1)
General disorders and administration site conditions	**25 (8.7)**	**19 (6.6)**	**13 (9.5)**	**10 (7.3)**
Fatigue	14 (4.9)	13 (4.5)	5 (3.6)	5 (3.6)
Asthenia	5 (1.7)	4 (1.4)	4 (2.9)	4 (2.9)
Blood and lymphatic system disorders	**24 (8.3)**	**23 (8.0)**	**22 (16.1)**	**21 (15.3)**
Neutropenia	18 (6.3)	18 (6.3)	20 (14.6)	19 (13.9)
Infections and infestations	**22 (7.6)**	**3 (1.0)**	**10 (7.3)**	**8 (5.8)**
Pneumonia	2 (0.7)	0	3 (2.2)	2 (1.5)
Paronychia	0	0	3 (2.2)	3 (2.2)
Respiratory, thoracic and mediastinal disorders	**18 (6.3)**	**11 (3.8)**	**6 (4.4)**	**3 (3.2)**
Dyspnoea	5 (1.7)	2 (0.7)	3 (2.2)	1 (0.7)
Gastrointestinal disorders	**15 (5.2)**	**6 (2.1)**	**23 (16.8)**	**20 (14.6)**
Diarrhoea	4 (1.4)	0	11 (8.0)	11 (8.0)
Abdominal pain	1 (0.3)	0	3 (2.2)	2 (1.5)
Vomiting	1 (0.3)	0	7 (5.1)	5 (3.6)
Nervous system disorders	**8 (2.8)**	**4 (1.4)**	**11 (8.0)**	**10 (7.3)**
Neuropathy peripheral	3 (1.0)	3 (1.0)	3 (2.2)	3 (2.2)
Skin and subcutaneous tissue disorders	**5 (1.7)**	**5 (1.7)**	**19 (13.9)**	**19 (13.9)**
Palmar-plantar erythrodysaesthesia syndrome	0	0	19 (13.9)	19 (13.9)

Note: dose modification includes dose delay and/or dose reduction
Note: dose modifications did not apply to oral drugs lapatinib and capecitabine
Note: AEs were coded using MedDRA version 23.1

The dose modifications due to a TEAE were more reported in the Physician's choice group than the SYD985 group in study SYD985.002 (i.e. 54.0% and 45.8%, respectively). The majority of TEAEs leading to dose modification in SYD985 arm were Eye disorders (22.0% vs 0 in the Physician's choice group) and included conjunctivitis (9.7%), keratitis (7.6%) and dry eye (3.1%).

In Study SYD985.001 in Part II, TEAEs leading to dose modifications in more than 5 patients were conjunctivitis (9.6%), neutropenia (8.9%), fatigue (4.8%), IRR (4.8%), dry eye (4.1%), and keratitis (4.1%), which was consistent with the study SYD985.002.

3.3.7.10. Post marketing experience

Not applicable.

3.3.8. Discussion on clinical safety

The key safety data derives from the pivotal controlled study phase III SYD985.002 (TULIP) that included 288 patients with HER2-positive unresectable locally advanced or metastatic breast cancer receiving at least one dose of SYD985 (trastuzumab duocarmazine) 1.2 mg/kg once every 3 weeks (Q3W). The median duration of exposure to trastuzumab duocarmazine was 4.8 months (range: 1-23) with the majority of subjects exposed between 0 to 6 months (65%) and 5.9% of subjects exposed >12 months. The median duration of exposure to trastuzumab duocarmazine is considered relatively short and limits the characterisation of the safety profile of trastuzumab duocarmazine. It is however reflective of the large rate of treatment discontinuation (98.2%) at the DLP mainly due to disease progression and adverse events.

The great majority of subjects included in the TULIP study experienced a TEAE, i.e. 97% in the trastuzumab duocarmazine group and 96% in the Physician's choice group. The eye disorders were the most frequently reported TEAEs with trastuzumab duocarmazine, i.e. 78.1% vs 29.2%. The most frequently TEAEs by PT observed in subjects treated with trastuzumab duocarmazine (>20%) group were conjunctivitis (38.2%, +36% compared to the Physician's group), keratitis (38.2%, +30.2%), Fatigue (33.3%, +3.4%), Dry eye (30.2%, +20%), Nausea (25.3%, -6.1%), Alopecia (21.5%, +9.8%), Decreased appetite (21.2%, +10.3%), Diarrhoea (20.8%, -15%), Asthenia (20.1%, +3.3%).

The Grade ≥3 TEAEs occurred at comparable rate between the two treatment arms in TULIP study (48% vs 53% in trastuzumab duocarmazine and Physician's choice groups, respectively). The Grade ≥3 Eye disorders were the most frequently reported in subjects treated with trastuzumab duocarmazine occurring in 21.2% subjects in the treatment arm vs 0 in the comparator arm, of which Grade ≥3 keratitis (12.2%), Grade ≥3 conjunctivitis (5.6%) and Grade ≥3 dry eyes (4.2%). The other most reported Grade ≥3 TEAEs occurring in >2% of patients in the trastuzumab duocarmazine arm were neutropenia (4.9%), fatigue (3.1%), anaemia (2.4%) and pneumonitis (2.1%) with higher incidence than the comparator except for neutropenia (4.9% for trastuzumab duocarmazine vs 18.2% for Physician's choice). Indeed, the haematotoxicity was more pronounced in the physician's choice arm compared to trastuzumab duocarmazine, i.e. 21.9% vs 8.7% of Grade ≥3 TEAEs from SOC Blood and lymphatic system disorders, respectively.

The dose calculation is body-weight based and weight change during treatment should be taken into account. Weight loss was observed in 10.1% patient treated with SYD985 compared with 1.5% patients treated with physician's choice and 3.1% SYD985 treated patients experienced the dose modification. In TULIP trial protocol, the patients with weight change >5% during the treatment need to recalculate the dose. Nearly 40% patient in SYD 985 arm had at least 1 time a change in weight of >5%. Of 55% patients, the dose was adjusted accordingly, the dose for 25% patients was adjusted but not completely in line with the instructions, and for 18 (16%) the dose was not adjusted. Some patients experienced multiple times of a weight change of >5%.

Among the SOC that were reported at a lower rate (<10%) in the phase 3 study, an imbalance is noted across the two treatment arms for the cardiac disorders, i.e. 10.1% vs 1.5% for TEAEs and 3.8% vs 0.7% for treatment-related TEAEs in the SYD985 arm and the physician's choice arm, respectively, including Pericardial effusion (3.5% vs 0 for TEAEs, 1.7% vs 0 for the treatment-related), Tachycardia (2.4% vs 0.7% for TEAEs, 0.7% vs 0 for the treatment-related) and Sinus tachycardia (1.4% vs 0 for TEAEs, 0.3% vs 0 for the treatment-related). Considering the higher reported tachycardia and sinus tachycardia AEs and the larger averaged mean heart rate change from baseline in the trastuzumab duocarmazine group compared to the Physician's choice treatment groups based on the ECG evaluation, the applicant was requested to further investigate the risk of trastuzumab duocarmazine on heart rate and update the section 4.8 accordingly. The detailed analysis performed by the applicant demonstrated a higher average increase in heart rate in subjects treated with SYD985 compared to physician's choice

with no evidence of a clinically significant effect. The TEAEs tachycardia and sinus tachycardia were more reported in SYD985 group than comparator (i.e. 2.4% vs 0.7%, respectively) and tachycardia was added to the list of ADRs in section 4.8 of the SmPC.

The AESIs determined for trastuzumab duocarmazine were Interstitial lung disease (ILD)/Pneumonitis of any grade, Severe ocular toxicity grade ≥ 3, Keratitis grade ≥ 2 and LVEF decrease to < 50%. They were based on previously observed safety signals with trastuzumab duocarmazine (ocular toxicity and ILD/pneumonitis) and/or general safety signals for HER2-targeting drugs (LVEF decrease and ILD/pneumonitis).

The ocular toxicity is the main toxicity associated to trastuzumab duocarmazine with a high incidence of eye disorders and a large imbalance in comparison to the Physician's choice group (78.1% vs 29.2% for the Eye disorders, respectively) and the majority of the ocular TEAEs reported in the trastuzumab duocarmazine group were considered treatment-related, i.e. 74.3%. The majority of the ocular events were low grade (27.8% Grade 1 and 29.2% Grade 2). Nevertheless, the occurrence of Grade ≥ 3 ocular events remained high in trastuzumab duocarmazine arm compared to the comparator arm, i.e. 21.2% vs 0, respectively, and keratitis was the most frequently Grade 3 ocular event reported with trastuzumab duocarmazine (12.2%). Two cases of Grade 4 ocular TEAEs were reported in TULIP study, i.e. one Grade 4 blindness and Grade 4 retinal detachment related to a metastasis and one case of Grade 4 keratitis that improved to Grade 1 occurring in a subject that experienced 3 treatment-related serious keratitis after the last dose of SYD985. The median time to onset of first ocular adverse event was 1.2 months with increasing severity over time up to 5.5 and 6.0 months for grade ≥3 conjunctivitis and keratitis, respectively. While the cases of Grade 2-3 conjunctivitis appears manageable with the dose modifications, the Grade 2 dry eyes and keratitis were recovered/resolved in 71.4% and 74.6% of cases, respectively, and the recovering/resolution of Grade 3 dry eye and keratitis reached 66.7% and 76.5% respectively based on the data provided in D120 LoQ responses (tables 67-69) but inconsistently with data from Table 70 (Grade 2 and Grade 3 dry eyes resolving in 38% and 50% of cases, grade 2 and 3 conjunctivitis in 70% and 100%, grade 2 and 3 keratitis in 43% and 62%, respectively) **(OC),** which supports the irreversibility of these ocular events in a non-negligible proportion of cases. A total of 52% of cases of Grade 2 keratitis occurring with Jivadco in TULIP study had no action taken and 15% led to a treatment discontinuation inconsistently with the mitigation measures per protocol; this needs to be further justified by the applicant **(OC).** It remains unclear the proportion of ocular events that had a complete resolution and those with partial improvement (i.e. decrease in severity by one or more grades from the worst grade) preventing the characterisation of the ocular toxicity; an overview of the outcomes of Grade ≥2 keratitis, conjunctivitis and dry eyes should be provided with a clear distinction between complete and partial resolution **(OC).** In addition, it was not clear if the incomplete/not reported outcomes of ocular toxicity AE were noted as "unknown" or "not resolved" considering that the applicant stated that cases were reported as ongoing at the time of censoring in the clinical database for incomplete information on resolution **(OC).** Time to full or incomplete resolution provided for grade ≥2 conjunctivitis, keratitis and dry eye were supportive of a slow resolution with a median duration of fully recovered grade 2 conjunctivitis and grade 3 keratitis of approximately 2 months (up to 725 day for grade 3 keratitis and 980 days for grade 2 conjunctivitis) and approximately 3 months for grade 3 conjunctivitis (up to 344 days) and grade 2 keratitis (up to 836 days). With regard to incompletely resolved ocular toxicity cases, the median duration was comprised between 1 and 2 years depending on the type of event and severity. For Grade 3 keratitis incompletely resolved, including 20% of not resolved cases, the median duration was 637 days (~ 1 year and 9 months) up to 1193 days. Moreover, the case of the SYD985-treated subject that reported 3 SAEs of keratitis shows the potential recurrence of serious ocular toxicity despite treatment discontinuation. The applicant was requested to justify its proposed recommendation to continue treatment in case of Grade 2 other ocular adverse reaction in light to the lower rate of resolution of Grade 2 ocular events compared to Grade 3 (42% and 64%, respectively)**.** It remained challenging to interpret the efficiency of the recommendation to continue treatment in case of

grade 2 other ocular AE considering the low rate of continuation of treatment of Grade 2 conjunctivitis and the resolution/recovering of only 48% of the Grade 2 dry eyes with no action taken. The concomitant ocular events occurring in subjects treated with SYD985 leading to one unique dose modification and the pooled outcomes of fully recovered/resolved and partially improved prevent a clear analysis of the mitigation measures for ocular toxicity and the distinction between a new ocular event and an ocular event that improved to a lower grade. The large percentage of treatment discontinuation due to ocular adverse reactions (i.e. 20.8%) observed in clinical studies is reflective of a poor tolerance of the ocular toxicity associated to trastuzumab duocarmazine.

A total of 71 (16.7%) enrolled patients (16.3% in SYD985 arm vs 17.5% in Physician's choice arm) with the medical history of eye disorders was reported in the pivotal trial. Similar ocular TEAEs including grade≥3 ocular AEs, serious ocular AEs, treatment discontinuation due to ocular AEs in the patients with/without a medical history of eye disorders in both arms are observed, not indicating currently that a medical history of eye disease is a risk of developing ocular disorders.

ILD/pneumonitis (including all terms) is a known risk with conjugated trastuzumab and was reported in 6.1% of patients treated with trastuzumab duocarmazine in any of the trials, all events reported as treatment-related. In study SYD985.002 (TULIP), 8.7% of subjects treated with trastuzumab duocarmazine experienced an ILD/pneumonitis compared to 0 in the Physician's choice arm. The incidence of ILD/pneumonitis in subjects treated with SYD985 is greater in the TULIP study in comparison to the other trials (2.7% in SYD985.001, 3.8% in SYD985.003 and 6.7% in SYD985.004); the imbalance in the rate of ILD/pneumonitis would be more likely due to the different treatment duration across the studies according to the applicant however no clear risk factor was identified. The majority of the reported ILD/pneumonitis reported in trastuzumab duocarmazine arm were low grade of severity, i.e. Grade 1-2 in 5.9% of subjects (n=17). The high rates of resolved Grade 2 and Grade 3 cases (93% and 80%, respectively) are in favour of a reversibility of events of ILD/pneumonitis. It is however observed a lower rate of resolution of Grade 1 case that occurred in 4 out 9 cases (44%) in the trastuzumab duocarmazine treated subjects. The applicant justified the lower rate of resolved Grade 1 ILD/pneumonitis cases compared to Grade 2-3 by the longer duration or difficulty to obtain a complete resolution of radiologic appearance from a Grade 1 case while Grade 2-3 are often considered resolved when further reported at a lower grade. The dose reduction of ILD/pneumonitis Grade 1 when resolution is greater than 28 days in the SmPC was added consistently with trastuzumab deruxtecan. The time to onset of ILD/pneumonitis was comparable across the severity of the event, i.e. median TTO of 4.1 months for Grade ≥1, 4.5 months for Grade ≥2 and 3.6 months for Grade ≥3. The duration of ILD/pneumonitis was long, i.e. median duration of 55 days, reflective of a slow resolution and a non-negligible rate of unresolved cases (38.2%), and heterogeneous among the severity of the events. In subjects treated with trastuzumab duocarmazine in all trials, there was 70% (24/34) of ILD/pneumonitis reported that resulted in treatment discontinuation, approximately one third of cases (32.3%) were serious including 4 cases of death due to ILD/pneumonitis (Grade 5 TEAEs) of which 2 in TULIP study. The addition of a warning on the risk of ILD/pneumonitis associated to trastuzumab duocarmazine is therefore supported based on the pulmonary toxicity observed in the clinical trials and the serious events including fatal outcomes.

The left ventricular ejection fraction decreased is a known risk in the HER2-targeting drugs including the conjugated trastuzumab and were reported in 4.7% of subjects treated with trastuzumab duocarmazine across the clinical trials with a majority of events that were Grade 2 in severity (2.5%), 0.7% of Grade 3 and one case (0.3%) of Grade 4. An imbalance of ejection fraction decreased between the trastuzumab duocarmazine and physician's choice arms was observed in TULIP study, i.e. 3.8% vs 0.7%, respectively. The risk of left ventricular ejection fraction decreased is considered manageable with a majority of the events that were reported with trastuzumab duocarmazine in the TULIP study that resolved (13/16) including all grade 3 and 4 events.

Deaths due to AEs occurred in 6 subjects in the trastuzumab duocarmazine group including 4 treatment-related vs 0 in the comparator in TULIP study, one subject in SYD985.001 study with was considered trastuzumab duocarmazine related, four subjects in study SYD985.003 that were considered non-related to trastuzumab duocarmazine and one subject in study SYD985.004 considered as treatment-related. Both treatment-related fatal AEs occurring with trastuzumab duocarmazine were respiratory events and mostly pneumonitis. A large imbalance of serious TEAEs was observed across the two treatment arms in TULIP study, i.e. 18.4% vs 8.8% in the trastuzumab duocarmazine arm and the Physician's choice arm, respectively. Similar to the fatal AEs, 'Respiratory, thoracic and mediastinal disorders' was the SOC with the most reported serious AEs in trastuzumab duocarmazine group (5.2%) in TULIP study and the most commonly reported serious TEAE by PT (>1%) was pneumonitis (2.4%). The majority of the serious TEAEs reported in the trastuzumab duocarmazine arm recovered/resolved with or without sequelae but the high rate of reported SAEs with trastuzumab duocarmazine including fatal cases is reflective of a worst safety profile than the comparator.

Overall, a worsening of haematological laboratory parameters from baseline was observed in subjects treated by trastuzumab duocarmazine in TULIP study (68.9% for low lymphocytes, 55.6% for low leukocytes, 42.1% for low haemoglobin, 22.3% for neutrophils and 20.4% for platelets, all grade) but generally Grade 1-2 and less pronounced than in the Physician's choice except for the lymphocytes low.

In TULIP study, the trastuzumab duocarmazine treated patient with mild (n=109) and moderate (n=12) renal impairment experienced more keratitis, dry eye and lacrimation increased than subjects with normal renal function (n=166). In addition, more cases of conjunctivitis were reported in moderate renal impaired subjects than subjects with normal renal function. Serious AEs were more reported in subjects treated with trastuzumab duocarmazine in the pivotal study with mild hepatic impairment compared to subjects with normal hepatic function (i.e. 25.3% and 14.6%, respectively). Concerning the use in pregnant women, according to human data on trastuzumab, it is expected that a teratogenic and fetotoxic risk will be observed in case of exposure during pregnancy. Therefore, Jivadco should not be used during pregnancy. It is noted that a period of contraception after discontinuation treatment should be used considering the mutagenic effect of SYD986. The t1/2 of SYD986 is 6 days. Therefore, a contraception period of 7 months in women of childbearing potential and 4 months in men with female partners of childbearing potential is acceptable. There were 6 (2.2%) patients treated with SYD985 in the TULIP study having treatment-emergent ADA of which one patient that reported three IRR AEs that were mild and moderate in severity and reversible. This low rate supports an acceptable impact of ADA on the safety profile of SYD985.

In the TULIP study, the rate of treatment discontinuation due to TEAEs was approximately 3-times higher in the trastuzumab duocarmazine group compared to the Physician's choice group, i.e. 35.4% vs 10.2% respectively, mainly driven by the eye disorders (20.8% vs 0). The dose modifications due to a TEAE were more reported in the Physician's choice group than the trastuzumab duocarmazine group in the TULIP study (i.e. 54.0% and 45.8%, respectively). To better identify the dose modifications that applied to the subjects treated with trastuzumab duocarmazine, a table summarizing the type of AEs by SOC and PT for each dose reduction schedule (0.9 mg/kg and 0.6 mg/kg) was requested. The majority of subjects treated with SYD985 in TULIP study that experienced a dose reduction due to a TEAE had one level dose reduction from 1.2 to 0.9 mg/kg (65 [23%] subjects), mainly ocular toxicity and a lower rate of subjects experienced a second dose reduction from 0.9 to 0.6 mg/kg due to TEAE, i.e. 9 (3%) subjects including 4 cases due to eye disorders. The majority of TEAEs leading to dose modification in trastuzumab duocarmazine arm were eye disorders (22.0% vs 0 in the Physician's choice group) and included conjunctivitis (9.7%), keratitis (7.6%) and dry eye (3.1%).

3.3.9. Conclusions on clinical safety

The safety profile of trastuzumab duocarmazine is primarily based on the data of the phase 3 study TULIP. The ocular toxicity is the main risk associated with trastuzumab duocarmazine with highly reported ocular disorders including severe keratitis with a limited improvement/resolution and is the most frequent toxicity leading to treatment discontinuation. The pulmonary toxicity is also of concern and represents the main cause of fatal AEs and other serious AEs with trastuzumab duocarmazine. The high occurrence of discontinuation of treatment due to AEs and serious AEs in subjects treated with trastuzumab duocarmazine is reflective of a poor tolerability in a study population with advanced breast cancer in a 2L+ setting and needs to be taken in consideration in the benefit-risk ratio.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Ocular toxicity ILD/ pneumonitis Left ventricular dysfunction
Important potential risks	Embryotoxicity
Missing information	Clinical outcomes in patients with severe renal impairment Clinical outcomes in patients with moderate and severe hepatic impairment

3.4.1.1. Discussion on safety specification

The safety specifications were modified upon D120 LoQ as follows:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Ocular toxicity ILD/ pneumonitis Left ventricular dysfunction
Important potential risks	Embryotoxicity Product confusion-related medication errors
Missing information	Use in patients with severe renal impairment Use in patients with moderate and severe hepatic impairment

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate provided medication error is included as important potential risk. As other trastuzumab-containing products are registered, there is a potential risk of medication errors which will have serious consequences of inadvertently substituting one product for another trastuzumab containing products.

3.4.2. Pharmacovigilance plan

3.4.2.1. Routine pharmacovigilance activities

The applicant proposed follow-up questionnaires for ocular toxicities, ILD/pneumonitis and product confusion-related medication error.

Considering that ocular toxicity is the main toxicity associated to trastuzumab duocarmazine with a high incidence of eye disorders in the clinical trials, it is considered highly unlikely that the information collected in the follow-up questionnaires will facilitate further characterisation of the risk. There is comprehensive information on the risk of ocular toxicity provided in SmPC section 4.8. including severity, time to onset, reversibility and potential risk factors. The PRAC Rapporteur does not expect that further characterisation via spontaneous reporting would lead to any changes to the clear and actionable information on this risk already in place in the proposed SmPC.

ILD/pneumonitis is an established risk for other trastuzumab-containing products and the PRAC Rapporteur does not anticipate any significant further characterisation via the collection of data proposed in the follow-up questionnaire beyond routine follow-up.

Regarding product confusion-related medication error, the follow-up questionnaire was proposed to evaluate the effectiveness of RMMs. This is not accepted (see section below).

The follow-up questionnaires for ocular toxicities, ILD/pneumonitis and product confusion-related medication error are not supported and should be removed from the RMP. (**OC**)

3.4.2.2. Summary of additional PhV activities

The applicant did not propose any additional pharmacovigilance activities.

Areas of missing information

Upon request, the applicant discussed that no additional clinical studies on patients with severe renal impairment and with moderate/severe hepatic impairment are considered necessary, considering the expected limited exposure in these patient populations and that hepatic elimination is expected to be limited. Furthermore, the applicant proposed to include a warning in section 4.4. of the SmPC to alert physicians to use the product with caution in these patient populations.

The PRAC Rapporteur would like to highlight that absence of data in these populations alone does not justify inclusion in the RMP list of safety concerns. Areas of missing information should only be included in case there is a reasonable expectation that the safety profile in such population may differ from that of the population studied in the clinical development. Inclusion in the RMP would therefore typically require additional pharmacovigilance activities to fill the gaps in knowledge regarding the safety profile in these populations.

Use in patients with moderate and severe hepatic impairment

In the two patients with moderate hepatic impairment included in clinical trials, an increased exposure of DUBA was observed. Based on request by the CHMP Rapporteur, this information was included in SmPC section 4.2. Moreover, section 4.8 was amended by the applicant to inform that serious adverse reactions were reported more frequently in patients treated with trastuzumab duocarmazine with mild hepatic impairment as compared to patients with normal hepatic function. Based on these limited data, there is a reasonable expectation that the safety profile would differ in patients with moderate and severe hepatic impairment, supporting the inclusion in the RMP list of safety concerns.

However, adequate risk minimisation measures are reflected in the SmPC, including:

- information in section 2.2 that an increased exposure of DUBA was observed in patients with moderate hepatic impairment,
- a warning in section 4.4 to alert physicians to use the product with caution in patients with moderate and severe hepatic impairment, and
- information in section 4.8 that serious adverse reactions were reported more frequently in patients with mild hepatic impairment as compared to patients with normal hepatic function.

Based on this, it is anticipated that physicians will be able to make informed decisions regarding the treatment of patients with moderate and severe hepatic impairment. Moreover, in view of a limited number of patients anticipated to be treated, an additional PhV activity to investigate the safety profile within this special population is not considered appropriate and proportionate to the importance of the potential risk related to patients with moderate and severe hepatic impairment. Routine PhV activities are considered adequate to monitor the safety of trastuzumab duocarmazine when used in patients with moderate and severe hepatic impairment.

Use in patients with severe renal impairment

As discussed in the response to Q109, patients with moderate renal impairment reported more often ocular adverse events and the applicant updated SmPC section 4.8 accordingly. Moreover limited data suggest a slight increase in exposure in patients with moderate renal impairment. Based on these data, there is a reasonable expectation that the safety profile would differ in patients with severe renal impairment, supporting the inclusion in the RMP list of safety concerns. However, adequate risk minimisation measures are reflected in the SmPC, including:

- a warning in section 4.4 to alert physicians to use the product with caution in patients with severe renal impairment, and
- information in section 4.8 that patients with mild and moderate renal impairment more frequently experienced ocular toxicities as compared to patients with normal renal function.

Based on this, it is anticipated that physicians will be able to make informed decisions regarding the treatment of patients with severe renal impairment. Moreover, in view of a limited number of patients anticipated to be treated, an additional PhV activity to investigate the safety profile within this special population is not considered appropriate and proportionate to the importance of the potential risk related to patients with severe renal impairment. Routine PhV activities are considered adequate to monitor the safety of trastuzumab duocarmazine when used in patients with severe renal impairment.

Evaluation of effectiveness of RMMs

The applicant proposed to use the follow-up questionnaires for evaluation of effectiveness of RMMs. This is not accepted, since these do not allow for any systematic evaluation. As dependent on spontaneous reporting, using follow-up questionnaires would threaten the validity of the evaluation of effectiveness as only those HCPs who observed and reported the adverse event for which the RMMs apply can participate. This would strongly bias any evaluation and unlikely provide true estimates on the effectiveness of the RMMs.

Evaluation of effectiveness of RMMs for ocular toxicity and ILD/pneumonitis

Based on the discussion at the PRAC plenary meeting, a study to evaluate the effectiveness of RMMs is not considered feasible. Routine PhV activities are considered sufficient to evaluate the effectiveness of the RMMs.

Evaluation of effectiveness of RMMs for product confusion-related medication error

Very similar aRMMs regarding the potential risk of product confusion-related medication error are in place for other trastuzumab-containing products and the risk seems to be well-managed according to recent PSURs (e.g. for Enhertu, no case has been reported since market introduction). Furthermore, no study to evaluate the effectiveness of these aRMMs is in place for other trastuzumab-containing products. Therefore, the PRAC Rapporteur considers evaluation of outcome indicators via routine PhV could be sufficient, as described for the other products: *"All cases representing potential product confusion-related medication errors in the postmarketing setting will be evaluated periodically in terms of frequency, involved drugs, root causes (if available) as well as clinical outcomes and will be presented in each Periodic Safety Update Report"*.

3.4.2.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considers that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

3.4.3.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Ocular toxicity	Routine risk communication : *SmPC sections: 4.2, 4.4, 4.7, 4.8* *Patient Leaflet (PL) sections 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: • Regular ophthalmic exams to be conducted prior to treatment initiation, prior to second infusion and subsequently prior to every other infusion, or as clinically indicated, as warranted in Section 4.4 of the SmPC. • Treatment interruption and dose reduction by one level are advised in case of Grade 2 keratitis. In case of Grade 3 keratitis, permanent discontinuation is recommended in Section 4.2 of the SmPC. • For all other ocular adverse reactions more than grade 3, dose reduction by one level and treatment interruption until the event is Grade 2 or less in severity or resolved is recommended in Section 4.2 of the SmPC. • Use of preservative-free lubricant eye drops starting with the first infusion and continuing until end of treatment is recommended in Section 4.4 of the SmPC. • Initiation of supportive treatment when signs and symptoms of ocular toxicity occur is recommended in Section 4.4 of the SmPC. • Referencing patients to ophthalmologist in case of any new or worsening ocular signs and symptoms is recommended in Section 4.4 of the SmPC. • Avoidance of contact lenses unless directed by an ophthalmologist throughout treatment is recommended in Section 4.4 of the SmPC.
	Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription

ILD / pneumonitis	Routine risk communication: *SmPC sections: 4.2, 4.4, 4.8* *PL sections: 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: • Patient monitoring for signs and symptoms of ILD/pneumonitis is recommended in Sections 4.4 of the SmPC. • Evaluating patients with suspected ILD/pneumonitis by radiographic imaging is recommended in Sections 4.4 of the SmPC. • Treatment interruption until resolved to Grade 0 is recommended for events of Grade 1 in severity, as described in Sections 4.2 and 4.4 of the SmPC. • Permanent treatment discontinuation in case of events of Grade ≥ 2 in severity is recommended in Sections 4.2 and 4.4 of the SmPC. • Corticosteroid therapy is to be considered for events of Grade 1 in severity and is to be promptly initiated for events of Grade ≥ 2 in severity, as warranted in Sections 4.2 and 4.4 of the SmPC. Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Left ventricular dysfunction	Routine risk communication: *SmPC sections: 4.2, 4.4, 4.8* *PL sections: 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: • LVEF should be assessed prior to initiation of trastuzumab duocarmazine and at regular intervals during treatment as clinically indicated, as recommended in Section 4.4 of SmPC. • In case of an absolute decrease of <10% from the baseline is observed, and LVEF is between 40% - 49%, LVEF assessment should be performed within 3 weeks, as recommended in Section 4.2 of the SmPC.

	• Treatment interruption in case an absolute decrease of ≥ 10% from the baseline is observed, and LVEF is between 40% - 49% is recommended in Section 4.2 of the SmPC. In case LVEF has not recovered to ≥50% and/or <10% from baseline, the treatment should be permanently discontinued. • Permanent treatment discontinuation in case of LVEF < 40% or clinically significant symptomatic cardiac disease is recommended in Section 4.2 and 4.4 of the SmPC. Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Important potential risks	
Embryotoxicity	Routine risk communication: *SmPC sections: 4.4, 4.6, 5.3* *PL section: 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • Women of childbearing potential should take a pregnancy test before treatment is initiated, as recommended in Sections 4.4 of the SmPC • Effective contraception is recommended for female patients during treatment and for 7 months following the last dose (see Sections 4.4 and 4.6 of the SmPC and section 2 of the PL) • Effective contraception is recommended for male patients with female partners of childbearing potential during treatment and for at least 4 months following the last dose (see Section 4.6 of the SmPC and Section 2 of the PL) Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Product confusion-related medication errors	Routine risk communication: *SmPC sections: 4.2, 4.4* *PL section: 6* Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information:
	• Legal status: restricted medical prescription

Missing information	
Use in patients with severe renal impairment	Routine risk communication *SmPC sections: 4.2, 4.4, 5.2* *PL section: 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription
Use in patients with moderate and severe hepatic impairment	Routine risk communication *SmPC sections: 4.2, 4.4, 5.2* *PL section: 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: restricted medical prescription

3.4.3.2. Summary of additional risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Ocular toxicity	Routine risk minimisation measures: *SmPC sections: 4.2, 4.4, 4.7, 4.8* *PL sections 2, 3, 4* Treatment should be adjusted or discontinued depending on the severity of the events. Monitoring of new or worsening ocular events. Regular ophthalmic exams to be conducted prior to treatment initiation, prior to second infusion and subsequently prior to every other infusion, or as clinically indicated. Use of preservative-free lubricant drops and avoidance of contact lenses throughout	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Ocular Toxicity Additional pharmacovigilance activities: None

	treatment. Avoidance of contact lenses. Restricted medical prescription. Additional risk minimisation measures: Prescriber´s Guide Patient´s Guide	
ILD/ pneumonitis	Routine risk minimisation measures: *SmPC sections: 4.2, 4.4, 4.8* *PL sections: 2, 3, 4* Treatment should be adjusted or discontinued depending on the severity of the events. Monitoring patients with suspected ILD/pneumonitis by radiographic imaging. Restricted medical prescription. Additional risk minimisation measures: Prescriber's Guide Patient's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Interstitial lung disease/pneumonitis Additional pharmacovigilance activities: None
Left ventricular dysfunction	Routine risk minimisation measures: *SmPC sections: 4.2, 4.4, 4.8* *PL sections: 2, 3, 4* Treatment should be adjusted or discontinued depending on the severity of the events. LVEF should be assessed prior to initiation of trastuzumab duocarmazine and at regular intervals during treatment as clinically indicated. Restricted medical prescription. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risks		
Embryotoxicity	Routine risk minimisation measures: *SmPC sections: 4.4, 4.6, 5.3* *PL section: 2*	Routine pharmacovigilance activities beyond adverse reactions

	A pregnancy test before treatment is initiated should be done in women of childbearing potential. Using effective contraception during treatment and for 7 months (female patients) or 4 months (male patients with female partners of childbearing potential) after the last dose of trastuzumab duocarmazine. Restricted medical prescription. Additional risk minimisation measures: None	reporting and signal detection: *None* Additional pharmacovigilance activities: None
Product confusion-related medication errors	Routine risk minimisation measures: *SmPC sections: 4.2, 4.4* *PL section: 6* Restricted medical prescription Additional risk minimisation measures: Prescriber's Guide Pharmacist's Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for product confusion-related medication errors Additional pharmacovigilance activities: None
Missing information		
Use in patients with severe renal impairment	Routine risk minimisation measures: *SmPC sections 4.2,4.4 5.2* *PL section 2* Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with moderate and severe hepatic impairment	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 5.2* *PL section 2* Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

The proposed risk minimisation activities are generally supported.

The applicant proposed to implement the risk of product confusion-related medication errors in the Prescriber's Guide. Moreover, the applicant proposed a Pharmacist's Guide as an additional educational material to warn pharmacists of the risk of product confusion-related medication errors during the dispensing process.

The PRAC Rapporteur supports to separate the healthcare professional target audience into prescribers and pharmacist and only to provide pharmacists with the information regarding product confusion-related medication errors. However, information on this risk is also relevant for other HCPs like the administering nurses, who are not covered by the two guides. The applicant is therefore requested to amend the Prescriber's Guide considering the following: The Prescriber's Guide should be called a Guide for HCPs and detailed information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase should also be communicated to nurses. (**OC**)

3.4.3.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures could be sufficient to minimise the risks of the product in the proposed indication(s), provided satisfactory responses to LoOI.

3.4.4. Protected Personal Data (PPD) and Commercially Confidential Information (CCI) considerations for the RMP Safety Specification

The RMP does not contain PPD/CCI.

3.4.5. PRAC Outcome

At the July 2023 PRAC plenary meeting the PRAC discussed Jivadco RMP version 0.2 and concluded the following:

- Safety specification: the revised summary of safety concerns including product-confusion related medication errors is supported.
- Pharmacovigilance plan: the PRAC supported the PRAC Rapporteur's assessment with regards to routine pharmacovigilance activities requiring the deletion of the proposed follow-up questionnaires for ocular toxicities, ILD/pneumonitis and product confusion-related medication errors.

  Besides the PRAC suggested that the possible need for additional pharmacokinetic studies in patients with moderate and severe hepatic impairment and patients with severe renal impairment may warrant further discussion by the CHMP. However, the

PRAC considered that PK studies would only allow collection of PK data and thus not inform sufficiently to further characterise the risks of Jivadco in these patient populations. Furthermore, additional Pharmacovigilance activities are not considered appropriate and proportionate to the importance of the potential risk related to patients with severe renal impairment and moderate and severe hepatic impairment, and monitoring via routine Pharmacovigilance is considered sufficient.

Regarding the evaluation of effectiveness of risk minimisation measures, the PRAC considered that the evaluation of outcome indicators via routine pharmacovigilance activities was sufficient. An additional pharmacovigilance activity for the evaluation of effectiveness of RMMs for ocular toxicity and ILD/pneumonitis was not considered necessary in this case.

- Risk minimisation activities: the PRAC supported the PRAC Rapporteur's assessment on the need for a guide for healthcare professionals and a patient guide to inform about the risks of ocular toxicity and ILD/pneumonitis. With regards to product confusion-related medication errors, the PRAC considered that the prescribers guide should be updated to target all relevant healthcare professionals including nurses and include detailed information about the dosage, method of administration and preparation as well as instructions to avoid medication errors during administration phase. The PRAC Rapporteur's request to include a guide for pharmacists to adequately inform of the risk of product confusion-related medication errors during the dispensing process was also supported.

In conclusion, the RMP for Jivadco (trastuzumab duocarmazine) in the proposed indication could be considered acceptable provided that an update to RMP version and satisfactory responses to the questions detailed in the joint CHMP-PRAC D150 overview assessment report (AR) are submitted. Upon assessment of the responses to the list of outstanding issues by the CHMP, the PRAC may consider that additional pharmacovigilance activities are warranted.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II,

Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD).

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The claimed indication for trastuzumab duocarmazine, as a single agent, is for the treatment of adult patients with HER2 (Human Epidermal Growth Factor Receptor 2)-positive breast cancer. Patients should have either:

- progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease, or
- progression during or after trastuzumab emtansine treatment in the locally advanced or metastatic setting.

5.1.2. Available therapies and unmet medical need

Metastatic HER2+ breast cancer is an incurable disease. Although treatment with anti-HER2-based regimens has improved the disease outcomes for patients with unresectable locally advanced or metastatic HER2-positive breast cancer, the disease invariably progresses. Treatment of patients after progression on T-DM1/T-DXd remains a clinical challenge, and the prognosis of these patients remains poor. In the proposed indication, for the treatment of patients with metastatic HER2+ breast cancer who have received for locally advanced or metastatic disease at least two HER2-targeting treatment regimens OR T-DM1, tucatinib + capecitabine + trastuzumab, T-DXd and T-DM1 appear to be the most active treatment options in the third-line setting and beyond. The choice of treatment depends on prior second-line therapy, patient characteristics (in particular brain metastases), toxicity profile and availability. In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET). If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, trastuzumab beyond progression should be considered.

5.1.3. Main clinical studies

The main evidence of efficacy submitted for the new active substance trastuzumab duocarmazine (also known as SYD985, Jivadco) is primarily based on the pivotal SYD985.002 study (TULIP), which is a multicentre, randomised, open-label, phase 3 clinical trial which compared the efficacy and safety of trastuzumab duocarmazine to physician's choice (TPC) in patients with HER2+ unresectable locally advanced or metastatic breast cancer. Results from this pivotal trial are supported by data from the Cohort A of the FIH phase I trial SYD985.001 in which patients with HER2+ breast cancer were treated with the intended dose regimen (1.2 mg/kg IV Q3W).

5.2. Favourable effects

- The primary endpoint of **PFS by IRC** was statistically significantly improved with SYD985 by 2.1 months in the FAS population, i.e. from 4.9 months to 7.0 months (HR 0.6401 (95%CI: 0.4885; 0.8389)). **Investigator-assessed PFS** as secondary endpoint was supportive (HR=0.5995 (95%CI: 0.4666, 0.7303, p-value <0.001). The KM curves separated early and kept being significantly separated in the observation time available. The sensitivity analyses were in line with the primary analysis of PFS by IRC.
- **PFS subgroup analyses** of efficacy of trastuzumab duocarmazine were consistent across all subgroups, with no clinically meaningful differences observed.

5.3. Uncertainties and limitations about favourable effects

- Patients in the physician's choice comparator treatment arm seemed to be more heavily pre-treated compared to those in the IMP arm, an imbalance which could have had a measure of influence on the outcome findings.
- The conduct of the pivotal study with respect to censoring in the PFS analysis on the discontinuation of study treatment, as well as the discontinuation of systematic follow-up of PFS at such intercurrent events result in substantial uncertainty with regards to the existence and extent of any PFS benefit compared to Physician's choice of treatments with limited efficacy. Moreover, the tipping point analysis of the applicant is not reassuring with regards to the robustness of the efficacy demonstration.

- OS would have been the preferable and feasible primary endpoint considering this late-stage setting population. However, it is agreed that the primary endpoint of PFS could be considered as an acceptable endpoint provided that a detrimental effect of the treatment on overall survival can be ruled out. The magnitude of the median PFS improvement of 2.1 months with trastuzumab duocarmazine compared to SoC is questioned given its potentially overestimated magnitude with no impact on secondary outcomes of OS and confirmed ORR per ICR.
- The applicant did not raise the OS secondary endpoint to the level of a key secondary endpoint, in deference of the CHMP scientific advice given. The OS curves and corresponding hazard ratio show a non-significant trend towards prolonged OS in the SYD985 group compared with the physician's choice group (hazard ratio (95% CI): 0.8680 (0.6760, 1.1145), p=0.236). The Kaplan Meier curves of the 2 arms cross each other which might suggest that at some point there might be an increased risk of death on SYD985.
- In the SYD985 group, 27.8% of patients with measurable disease at baseline were responders (confirmed plus unconfirmed) compared with 29.5% of patients in the physician's choice group. This difference was not statistically significant (p=0,732). A comparable proportion of patients who had measurable disease achieved confirmed complete response (CR) ICR assessed between the two treatment arms (2.0% versus 0.8% respectively) as well as patients who achieved confirmed partial response (PR) ICR assessed (18.3% versus 20.5% respectively).
- Improving patient quality of life is of great relevance for late stage setting. However, presented PRO data are considered difficult to interpret given the open label design of the study.
- The magnitude of the intracranial activity is currently uncertain, only about 12% of patients with stable metastases were enrolled in the study. Results should be interpreted with caution.

- Given the concurrent development of SYD985 with T-DXd (2L, Destiny Breast 03), patients in TULIP did not receive T-DXd prior to inclusion. The assessment of the benefit risk balance of SYD985 following a treatment with T-DXd is not possible.
- A routine GCP inspection identified critical findings on the sponsor's lack of access to source data from 12 of the 78 clinical sites, representing 75 patients out of 473, leading to GCP uncompliant monitoring of these sites and potentially impairing data integrity. Beyond centrally assessed/reviewed endpoints, these findings could affect reliability of the reporting including safety (due to potential underreporting outcomes).

5.4. Unfavourable effects

- The **ocular toxicity** was highly reported trastuzumab duocarmazine with a large imbalance of the incidence of eye disorders in comparison to the Physician's choice group in TULIP study, i.e. 78.1% and 29.2%, respectively. The great majority of the ocular TEAEs reported in the trastuzumab duocarmazine group were considered treatment-related, i.e. 74.3%. Grade ≥ 3 ocular events occurred in 21.2% of subjects treated with trastuzumab duocarmazine compared to 0 in the Physician's choice arm and keratitis was the most frequently Grade 3 ocular event reported with trastuzumab duocarmazine (12.2%).
- **Interstitial lung disease (ILD) and/or pneumonitis** occurred more frequently in subjects treated with trastuzumab duocarmazine compared to the Physician's choice arm in the TULIP study, i.e. 8.7% and 0, respectively and were reported in 6.1% of patients treated with trastuzumab duocarmazine in any of the trials, all events reported as treatment-related. A total of 70% of the ILD/pneumonitis reported cases in subjects treated with trastuzumab duocarmazine across all trials resulted in treatment discontinuation, approximately one third of cases (32.3%) were serious including 4 deaths due to ILD/pneumonitis of which 2 in TULIP study.
- **Serious adverse events** were reported approximately 2-times more with trastuzumab duocarmazine compared to the Physician's choice arm in the TULIP study, i.e. 18.4% and 8.8%, respectively. Deaths due to AEs were also more reported within trastuzumab duocarmazine than the comparator in the TULIP study, i.e. 6 subjects including 4 treatment-related vs 0, respectively. All the fatal cases treatment-related and the majority of the serious TEAEs reported in the trastuzumab duocarmazine were associated to pulmonary toxicity; the most frequent reported fatal adverse event was pneumonitis.
- The **treatment discontinuations due to TEAEs** were approximately 3-times higher in the trastuzumab duocarmazine group compared to the Physician's choice group in the TULIP study, i.e. 35.4% vs 10.2% respectively. This high rate of TEAEs leading to the discontinuation of trastuzumab duocarmazine was mainly driven by the eye disorders (20.8%).

5.5. Uncertainties and limitations about unfavourable effects

- Uncertainties remain on the **reversibility of the ocular toxicity**, considering the limited rate of resolution/recovering of the Grade 2 and 3 Keratitis and the Grade 2 and 3 Dry eyes despite the treatment discontinuation and dose modifications due to ocular disorders reported in 20.8% and 22.0% of subjects treated with trastuzumab duocarmazine in TULIP study, respectively. Also, no distinction between the cases of ocular toxicity that were fully recovered and partially improved to a lower grade was done in the cases that resolved/recovered. Moreover, the recovery of ocular toxicity may take weeks to months in particular for higher grade events in an intended population with advanced or metastatic breast cancer in a late setting line of treatment.

- The **efficiency of the proposed mitigation measures for the ocular toxicity** is uncertain. The analysis of the proposed mitigation measures remains challenging considering that a part of the eye disorder events occurring in TULIP study in subjects treated with SYD985 were not managed as per protocol likely due to concomitant ocular events for a part of the cases.
- The greater incidence of ILD/pneumonitis in subjects treated with trastuzumab duocarmazine in the TULIP study compared to the other clinical trials is not explained in the **lack of identified risk factor.**
- No safety data were collected on **severe renal impaired** and **moderate and severe hepatic impaired** subjects.

5.6. Effects Table

Table 60: Effects Table for trastuzumab duocarmazine for HER2+advanced breast cancer (data cut-off: 31 March 2021).

Effect	Short Description	Unit	Treatment SYD985	Control TPC	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by IRC	ICR-assessed Progression-free survival	Months (95%CI)	7.0 (5.4; 7.2)	4.9 (4.0; 5.5)	Potentially overestimated magnitude	FAS pop N=437
			HR 0.64 (0.49, 0.84) p<0.002			
OS	Overall survival	Months (95%CI)	21.0 (18.1; 25.0)	19.5 (14.2; 23.1)	Final OS data Not statistically significant	FAS pop N=437
			HR = 0.87 (0.68, 1.11) P=0.24			
ORR	ICR-assessed best overall response of CR or PR	% (95%CI)	27.8 (30.0; 39.5)	29.5 (14.1; 25.4)	Not statistically significant	N= 374 with measurable disease
			p=0.73			
Unfavourable Effects						
Eye disorders All grade		%	78.1	29.2	Mainly driven by conjunctivitis and keratitis	TULIP study
ILD/pneumonitis All grade		%	8.7	0	Two (0.7%) deaths and 7 (2.4%) SAEs in the SYD985 arm	
SAEs		%	18.4	8.8		
TEAEs leading to treatment discontinuation		%	35.4	10.2	Mainly driven by conjunctivitis and keratitis	

Abbreviations: PR: Partial Response; CR: Complete response; SAE: Serious adverse event; TEAE: treatment-emergent adverse event

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The magnitude of the median PFS improvement of 2.1 months with trastuzumab duocarmazine compared to SoC is considered not sufficient given its potentially overestimated magnitude (see major objections) and given the lack of impact on important secondary outcomes of OS and ORR per ICR (which showed no difference between the two arms and was numerically lower on the SYD985 arm: 20.2% on SYD985 vs. 21.3% on Physician's Choice) and the observed safety profile of SYD985 (e.g. ocular toxicity including severe keratitis leading to a large rate of treatment discontinuation, life-threatening pulmonary toxicity leading to a high rate of serious adverse events including death, impact of these adverse events in particular resolvability and their management). The benefit in PFS appears to be uncertain and partly driven by a larger number of patients experiencing SD disease under SYD985 treatment (47.6%) vs PC (36.9%). The translation of this benefit in terms of OS remains uncertain. Even though in this very advanced setting, where the tumour burden is important, ORR would translate into a greater benefit in the patient perspective, an improvement in the SD rate could be of interest, provided that it favourably compares to the standard treatment in terms of tolerability. However, the important toxicities observed, notably in terms of ocular events but also including ILD/pneumonitis and left ventricular ejection fraction decreased, remain a challenge and could outweigh the limited benefit outlined above.

The characterisation of the ocular toxicity is prevented by the lack of distinction between the ocular events that had a complete resolution and those with a partial improvement (i.e. decrease in severity by one or more grades from the worst grade) that could not inform on the reversibility of the toxicity. The analysis of the proposed mitigation measures for the ocular toxicity remains challenging considering that a part of the eye disorder events occurring in TULIP study in subjects treated with SYD985 were not managed as per protocol likely due to concomitant ocular events which prevent the assessment of their efficiency to manage the ocular toxicity. Indeed 14.8% of Grade 2 dry eyes, 41.5% of Grade 2 conjunctivitis and 67.2% Grade 2 keratitis did not receive the appropriate mitigation measure as per protocol. Also, most of Grade 3 dry eyes and conjunctivitis cases led to a treatment discontinuation (58.3% and 55.6%, respectively) inconsistently with the dose management as per protocol. Moreover, the rate of 21% of Grade 3 keratitis not resolved/recovered further to the discontinuation of treatment suggests this toxicity is poorly manageable and still raise uncertainties on the tolerability of SYD985 in a heavily pre-treated population with advanced cancer. Final OS result might suggest that the higher toxicity observed with SYD985 does not have any unfavourable effect on patient survival. However, this interpretation is questionable, as the assumption of a constant HR over time supporting this result is highly unlikely in the updated survival data. Complementary OS analyses accounting for non-proportional HR provided by the sponsor raise some concerns over an 8-month period (4-12 months) where an increased risk of death is observed under SYD985 as compared to control (Cox model analysis: HR=1.69, 95% CI [1.04; 2.50], P=0.034 / RMST analysis: 1 month less survival, 95% CI [-1.9 mo, 0.12 mo], P=0.026). It is therefore difficult to rule out any effect of treatment discontinuations for toxicity on this 8-month period with higher risk of death. It is also understood that after this 8-month period, only responders who can tolerate SYD985 still remained on treatment. This precludes any meaningful conclusion on OS thereafter.

No negative effect on HRQoL has been observed in SYD985.002 trial however due to the open-label design prone to bias and the nature of the outcome (exploratory), presented PRO data are considered difficult to interpret and no formal conclusion on HRQoL can be made.

5.7.2. Balance of benefits and risks

The questionable gain in PFS has to be weighed against an important toxicity profile, including ocular toxicities that were not observed with other HER2-targeting ADCs. This challenging tolerance profile is of particular importance in this late line setting where quality of life takes increasing importance for patients.

Due to the study conduct regarding assessment and analysis of PFS, the presence and extent of any superiority over the control arm is unclear. Also, when taking the PFS outcome of the primary analysis at face value, it is difficult to ascertain that the benefits of Jivadco outweighs safety concerns. These include fatal cases of pneumonitis, as well as common ocular adverse effects. This is mainly keratitis, frequently described as non-resolved despite treatment discontinuation, and occasionally resulting in blindness.

Furthermore, beyond centrally assessed/reviewed endpoints, the GCP inspection findings could affect reliability of the reporting including safety (due to potential underreporting outcomes).

The benefit of trastuzumab duocarmazine in the claimed indication is negative.

5.7.3. Additional considerations on the benefit-risk balance

None.

5.8. Conclusions

The overall risk balance of trastuzumab duocarmazine is negative (see Major objections).

6. Appendices

6.1. AR on New Active Substance Claim dated 3 November 2022

Problem statement

This application was submitted in accordance with Article 8(3) of Directive 2001/83/EC and it contained evidence and discussion as to why the active substance trastuzumab duocarmazine should be regarded as new.

The applicant requested the active substance trastuzumab duocarmazine contained in the above medicinal product to be considered a new active substance in itself.

applicant's justification:

The active substance (INN: trastuzumab duocarmazine) is an antibody-drug conjugate (ADC) comprised of the Human Epidermal growth factor Receptor 2 (HER2)-targeting antibody trastuzumab (SYD977) covalently bound to a linker-drug (SYD980). The monoclonal antibody (SYD977) is produced in Chinese Hamster Ovary (CHO) cells and, after purification, is conjugated to SYD980 resulting in the ADC trastuzumab duocarmazine.

Trastuzumab duocarmazine is an active substance for human use for the treatment of adult patients with HER2-positive metastatic breast cancer. It is not previously authorised in the European Union (or any other country) and as such is considered to be a new active substance as defined in Annex I of EudraLex - Volume 2A - Procedures for marketing authorisation – Chapter 1 – Marketing Authorisation.

Discussion on quality aspects

Evidence to justify the status of trastuzumab duocarmazine as a new active substance (NAS) is provided in the annex 5.23 to MAA application form.

The applicant's justification for the claim of new active substance status is based on 1st indent of Annex I of Chapter 1 of Volume A of the Notice to applicants (NtA) (..*"a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union").*

Although it is acknowledged that trastuzumab duocarmazine is a molecule currently not included in any product authorised in the European Union, the applicant had further supported the NAS claim with comparative results showing that trastuzumab duocarmazine is substance–unrelated to any product previously authorised in the European Union. The official database queried for the sequence searches has been declared and justified.

Conclusions on quality aspects

The applicant's claim that trastuzumab duocarmazine is a new active substance has been further supported by the applicant and is endorsed.

The applicant has further substantiated the New Active Substance claim with comparative results showing that trastuzumab duocarmazine differs from any active substances previously authorised as part of a medicinal product in the European Union. As part of this substantiation, the applicant has conducted a search in an established database on structurally similar compounds to ensure that INN is a unique molecule. The official database queried for the sequence searches were identified and justified.