



Clinical trial results:

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

Summary

EudraCT number	2017-001994-18
Trial protocol	ES NL SE GB DK BE IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023

Trial information

Trial identification

Sponsor protocol code	SYD985.002
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03262935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Byondis BV
Sponsor organisation address	Microweg 22, Nijmegen, Netherlands, 6545 CM
Public contact	Clinical Development, Byondis BV, 0031 246795101, clinicaltrials@byondis.com
Scientific contact	Clinical Development, Byondis BV, 0031 246795101, clinicaltrials@byondis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This multi-centre, open-label, randomized, phase III clinical trial compared 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. Patients were randomized 2:1 to receive either SYD985 1.2 mg/kg via intravenous infusion every 3 weeks or physician's choice (PC; lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + vinorelbine, or trastuzumab + eribulin) administered per SmPC/PI until disease progression (PD), unacceptable toxicity, or withdrawal of consent. Patients who discontinued trial treatment were followed for survival until death, lost to follow-up, or withdrawal of consent.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Singapore: 35
Country: Number of subjects enrolled	United States: 53
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 59
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Italy: 70
Worldwide total number of subjects	437
EEA total number of subjects	266

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	332
From 65 to 84 years	104
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 751 participants were screened, out of which, 437 participants were randomized into the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SYD985

Arm description:

SYD985 1.2 mg/kg was administered every three weeks by intravenous infusion until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	SYD985
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

SYD985 1.2 mg/kg was administered every 3 weeks via intravenous infusion

Arm title	Physician's choice
------------------	--------------------

Arm description:

Physician's choice therapy options included: Lapatinib + Capecitabine, Trastuzumab + Capecitabine, Trastuzumab + Vinorelbine, or Trastuzumab + Eribulin. The physician's choice therapy was administered as per the SmPC/PI. Patients were treated until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lapatinib was administered as per the SmPC/PI

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered as per the SmPC/PI.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Trastuzumab was administered as per the SmPC/PI.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Vinorelbine was administered as per the SmPC/PI.

Investigational medicinal product name	Eribulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin was administered as per the SmPC/PI.

Number of subjects in period 1	SYD985	Physician's choice
Started	291	146
Completed	0	0
Not completed	291	146
Consent withdrawn by subject	6	7
End Of Follow Up By Sponsor	90	41
Death	181	94
Other	5	-
Lost to follow-up	9	4

Baseline characteristics

Reporting groups

Reporting group title	SYD985
-----------------------	--------

Reporting group description:

SYD985 1.2 mg/kg was administered every three weeks by intravenous infusion until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Reporting group title	Physician's choice
-----------------------	--------------------

Reporting group description:

Physician's choice therapy options included: Lapatinib + Capecitabine, Trastuzumab + Capecitabine, Trastuzumab + Vinorelbine, or Trastuzumab + Eribulin. The physician's choice therapy was administered as per the SmPC/PI. Patients were treated until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Reporting group values	SYD985	Physician's choice	Total
Number of subjects	291	146	437
Age categorical			
Units: Subjects			
Adults (18-64 years)	225	107	332
From 65-84 years	66	38	104
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	55.9	57.3	
standard deviation	± 11.2	± 10.97	-
Gender categorical			
Units: Subjects			
Female	291	146	437
Male	0	0	0

End points

End points reporting groups

Reporting group title	SYD985
Reporting group description: SYD985 1.2 mg/kg was administered every three weeks by intravenous infusion until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Physician's choice
Reporting group description: Physician's choice therapy options included: Lapatinib + Capecitabine, Trastuzumab + Capecitabine, Trastuzumab + Vinorelbine, or Trastuzumab + Eribulin. The physician's choice therapy was administered as per the SmPC/PI. Patients were treated until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description: The primary endpoint was PFS and was defined as the time (in months) from the date of randomization to the date of first documented disease progression as assessed by ICR according to RECIST v1.1 or death due to any cause (whichever occurred earlier). Full-analysis set (FAS) was used for this primary endpoint analysis. FAS comprises all randomized patients, which were analyzed according to the treatment group and strata they have been assigned to during the randomization procedure.	
End point type	Primary
End point timeframe: baseline until primary analysis data cut-off date of 31March2021	

End point values	SYD985	Physician's choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	146		
Units: months				
median (confidence interval 95%)	7.0 (5.4 to 7.2)	4.9 (4.0 to 5.5)		

Statistical analyses

Statistical analysis title	Stratified Cox regression analysis
Statistical analysis description: A stratified Cox regression analysis was used to estimate the hazard ratio of PFS, along with 95% CIs. Stratification factors assigned at randomization were world region (Europe, Singapore, and North America), number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (1 to 2, >2), and prior treatment with pertuzumab (yes, no).	
Comparison groups	SYD985 v Physician's choice

Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6401
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4885
upper limit	0.8389

Notes:

[1] - P-value from stratified log-rank test for median estimate of PFS: stratified according to the randomization stratification factors.

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall Survival was defined as the time from the date of randomization to the date of death due to any cause. Full-analysis set (FAS) was used for the overall survival analysis. FAS comprises all randomized patients, which were analyzed according to the treatment group and strata they have been assigned to during the randomization procedure.	
End point type	Secondary
End point timeframe:	
baseline until final Overall Survival analysis data cut-off date of 30June2022	

End point values	SYD985	Physician's choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	146		
Units: months				
median (confidence interval 95%)	21.0 (18.1 to 25.0)	19.5 (14.2 to 23.1)		

Statistical analyses

Statistical analysis title	Stratified Cox regression analysis
Statistical analysis description:	
A stratified Cox regression analysis was used to estimate the hazard ratio of OS, along with 95% CIs. Stratification factors assigned at randomization were world region (Europe, Singapore, and North America), number of prior treatment lines for locally advanced or metastatic breast cancer (excluding hormone therapy) (1 to 2, >2), and prior treatment with pertuzumab (yes, no).	
Comparison groups	SYD985 v Physician's choice

Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.676
upper limit	1.1145

Notes:

[2] - P-value from stratified log-rank test for Kaplan-Meier estimate of median OS: stratified according to the randomization stratification factors.

Secondary: Objective Response Rate on the basis of the blinded independent central review

End point title	Objective Response Rate on the basis of the blinded independent central review
-----------------	--

End point description:

Objective response rate was defined as the percentage of patients with ICR-assessed best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 (i.e. 'Responders'). Only patients with measurable disease at baseline were included in the analysis of ORR. Patients without a post-baseline tumour assessment were considered non-responders. Full-analysis set (FAS) was used for this primary endpoint analysis. FAS comprises all randomized patients, which were analyzed according to the treatment group and strata they have been assigned to during the randomization procedure.

End point type	Secondary
----------------	-----------

End point timeframe:

baseline until primary analysis data cut-off date of 31March2021

End point values	SYD985	Physician's choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	122		
Units: percentage of patients				
number (confidence interval 95%)	27.8 (22.3 to 33.7)	29.5 (21.6 to 38.4)		

Statistical analyses

Statistical analysis title	The Cochran-Mantel-Haenszel test
----------------------------	----------------------------------

Statistical analysis description:

The Cochran-Mantel-Haenszel test (strata based on the baseline stratification factors) was used to compare the two treatment groups with respect to the ORR at two-sided 5% level of significance.

Comparison groups	SYD985 v Physician's choice
-------------------	-----------------------------

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.732 ^[3]
Method	Cochran-Mantel-Haenszel
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - P-value from Cochran-Mantel-Haenszel test including the randomization stratification factors.

Secondary: Investigator Assessed Progression-Free Survival

End point title	Investigator Assessed Progression-Free Survival
-----------------	---

End point description:

Investigator assessed PFS, based on local review data captured in the eCRF, was defined as the time (in months) from the date of randomization to the date of first documented investigator-assessed disease progression according to RECIST 1.1 or death due to any cause (whichever occurs earlier). Full-analysis set (FAS) was used for this primary endpoint analysis. FAS comprises all randomized patients, which were analyzed according to the treatment group and strata they have been assigned to during the randomization procedure.

End point type	Secondary
----------------	-----------

End point timeframe:

baseline until primary analysis data cut-off date of 31March2021

End point values	SYD985	Physician's choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	146		
Units: months				
median (confidence interval 95%)	6.9 (6.0 to 7.2)	4.6 (4.0 to 5.6)		

Statistical analyses

Statistical analysis title	Stratified Cox regression analysis
----------------------------	------------------------------------

Statistical analysis description:

A stratified Cox regression analysis was used to estimate the HR of PFS, along with the 95% CI. The treatment groups were compared using the 2-sided stratified log-rank test.

Comparison groups	SYD985 v Physician's choice
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5995

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4666
upper limit	0.7703

Notes:

[4] - P-value from stratified log-rank test for median estimate of PFS: stratified according to the randomization stratification factors.

Secondary: Patient reported outcomes for health related quality of life

End point title	Patient reported outcomes for health related quality of life
-----------------	--

End point description:

In a MMRM analysis, the influence of various factors on the change in QoL scale score of the EORTC QLQ-C30 from baseline was assessed in the FAS. Factors evaluated in the model were treatment and cycle (both fixed effects), randomization strata (ie, world region, prior treatment lines for LABC or MBC, and prior treatment with pertuzumab), QoL scale score at baseline (covariate), and treatment-by-cycle (interaction). The factors treatment, randomization strata, and treatment-by-cycle did not have a significant effect on QoL scores. With a p-value of <0.001 for QoL scale score at baseline, it can be concluded that including baseline in the model is sensible. With a p-value of 0.002 for cycle, it can be concluded that there are differences in scores between the cycles. As the interaction between treatment and cycle was not significant (p=0.473), it can be concluded that the differences within the cycles are similar for both treatment groups.

End point type	Secondary
----------------	-----------

End point timeframe:

baseline until primary analysis data cut-off date of 31March2021

End point values	SYD985	Physician's choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	146		
Units: change in QoL scale score from baseline				
least squares mean (confidence interval 95%)				
C2	0.17 (-2.70 to 3.04)	-3.88 (-7.79 to 0.03)		
C3	-1.88 (-4.83 to 1.07)	-2.99 (-7.00 to 1.02)		
C4	-2.48 (-5.46 to 0.50)	-9.01 (-13.23 to -4.80)		
C5	-2.51 (-5.69 to 0.67)	-5.77 (-10.34 to -1.21)		
C7	-5.65 (-9.19 to -2.10)	-6.75 (-11.92 to -1.58)		
C9	-8.14 (-12.27 to -4.02)	-11.25 (-17.41 to -5.09)		
C11	-10.70 (-15.66 to -5.75)	-10.38 (-18.08 to -2.69)		
C13	-13.40 (-20.31 to -6.48)	-12.89 (-21.33 to -4.45)		
C15	-11.90 (-20.41 to -3.39)	-14.12 (-23.91 to -4.33)		
C17	-4.31 (-14.48 to 5.86)	-0.71 (-13.26 to 11.83)		
C19	-5.45 (-21.05 to 10.16)	1.66 (-13.84 to 17.16)		

C21	11.68 (-9.76 to 33.12)	-11.23 (-26.16 to 3.71)		
C23	5.30 (-26.04 to 36.65)	-7.00 (-29.18 to 15.17)		
C25	18.76 (-14.63 to 52.16)	-11.48 (-42.96 to 19.99)		
C27	0.49 (-33.40 to 34.37)	-5.41 (-38.83 to 28.02)		
C29	999 (999 to 999)	-6.54 (-40.45 to 27.37)		
C33	999 (999 to 999)	-7.11 (-41.14 to 26.92)		
C35	999 (999 to 999)	-15.73 (-49.79 to 18.33)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from signing of the ICF up to the treatment discontinuation visit. The safety data reported here is based on data collected up to the data cut off date of 31 March 2021.

Adverse event reporting additional description:

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

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	SYD985
-----------------------	--------

Reporting group description:

SYD985 1.2 mg/kg was administered every three weeks by intravenous infusion until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Reporting group title	Physician's choice
-----------------------	--------------------

Reporting group description:

Physician's choice therapy options included: Lapatinib + Capecitabine, Trastuzumab + Capecitabine, Trastuzumab + Vinorelbine, or Trastuzumab + Eribulin. The physician's choice therapy was administered as per the SmPC/PI. Patients were treated until disease progression (as assessed by the investigator), unacceptable toxicity, or withdrawal of consent.

Serious adverse events	SYD985	Physician's choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 288 (18.40%)	12 / 137 (8.76%)	
number of deaths (all causes)	181	94	
number of deaths resulting from adverse events	6	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic tumour necrosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			

subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			

subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	7 / 288 (2.43%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 288 (0.35%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 288 (0.00%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 288 (0.35%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcus test positive subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Keratitis			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 288 (0.35%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Livedo reticularis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 288 (1.04%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Wound infection			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 288 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SYD985	Physician's choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	278 / 288 (96.53%)	132 / 137 (96.35%)	
Investigations			
Weight decreased			
subjects affected / exposed	29 / 288 (10.07%)	2 / 137 (1.46%)	
occurrences (all)	45	2	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 288 (5.56%)	10 / 137 (7.30%)	
occurrences (all)	26	14	
Platelet count decreased			
subjects affected / exposed	16 / 288 (5.56%)	0 / 137 (0.00%)	
occurrences (all)	28	0	
Neutrophil count decreased			

subjects affected / exposed	14 / 288 (4.86%)	14 / 137 (10.22%)	
occurrences (all)	25	26	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 288 (4.17%)	10 / 137 (7.30%)	
occurrences (all)	19	17	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 288 (11.46%)	16 / 137 (11.68%)	
occurrences (all)	37	23	
Dysgeusia			
subjects affected / exposed	22 / 288 (7.64%)	4 / 137 (2.92%)	
occurrences (all)	26	5	
Dizziness			
subjects affected / exposed	21 / 288 (7.29%)	7 / 137 (5.11%)	
occurrences (all)	22	7	
Neuropathy peripheral			
subjects affected / exposed	16 / 288 (5.56%)	8 / 137 (5.84%)	
occurrences (all)	29	16	
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 288 (1.74%)	7 / 137 (5.11%)	
occurrences (all)	7	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	96 / 288 (33.33%)	41 / 137 (29.93%)	
occurrences (all)	162	66	
Asthenia			
subjects affected / exposed	58 / 288 (20.14%)	23 / 137 (16.79%)	
occurrences (all)	91	34	
Pyrexia			
subjects affected / exposed	23 / 288 (7.99%)	13 / 137 (9.49%)	
occurrences (all)	26	15	
Oedema peripheral			
subjects affected / exposed	22 / 288 (7.64%)	3 / 137 (2.19%)	
occurrences (all)	30	4	
Mucosal inflammation			

subjects affected / exposed occurrences (all)	17 / 288 (5.90%) 20	8 / 137 (5.84%) 10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 288 (14.24%)	17 / 137 (12.41%)	
occurrences (all)	85	35	
Neutropenia			
subjects affected / exposed	31 / 288 (10.76%)	33 / 137 (24.09%)	
occurrences (all)	75	76	
Thrombocytopenia			
subjects affected / exposed	17 / 288 (5.90%)	7 / 137 (5.11%)	
occurrences (all)	23	13	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	110 / 288 (38.19%)	3 / 137 (2.19%)	
occurrences (all)	218	3	
Keratitis			
subjects affected / exposed	110 / 288 (38.19%)	11 / 137 (8.03%)	
occurrences (all)	202	11	
Dry eye			
subjects affected / exposed	87 / 288 (30.21%)	14 / 137 (10.22%)	
occurrences (all)	117	15	
Lacrimation increased			
subjects affected / exposed	53 / 288 (18.40%)	2 / 137 (1.46%)	
occurrences (all)	74	2	
Blepharitis			
subjects affected / exposed	36 / 288 (12.50%)	2 / 137 (1.46%)	
occurrences (all)	53	2	
Punctate keratitis			
subjects affected / exposed	32 / 288 (11.11%)	3 / 137 (2.19%)	
occurrences (all)	45	4	
Vision blurred			
subjects affected / exposed	23 / 288 (7.99%)	1 / 137 (0.73%)	
occurrences (all)	30	1	
Periorbital oedema			

subjects affected / exposed occurrences (all)	17 / 288 (5.90%) 29	0 / 137 (0.00%) 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	73 / 288 (25.35%)	43 / 137 (31.39%)	
occurrences (all)	103	64	
Diarrhoea			
subjects affected / exposed	60 / 288 (20.83%)	49 / 137 (35.77%)	
occurrences (all)	82	92	
Constipation			
subjects affected / exposed	57 / 288 (19.79%)	24 / 137 (17.52%)	
occurrences (all)	74	28	
Vomiting			
subjects affected / exposed	36 / 288 (12.50%)	23 / 137 (16.79%)	
occurrences (all)	52	37	
Dry mouth			
subjects affected / exposed	26 / 288 (9.03%)	6 / 137 (4.38%)	
occurrences (all)	28	6	
Stomatitis			
subjects affected / exposed	24 / 288 (8.33%)	17 / 137 (12.41%)	
occurrences (all)	34	17	
Abdominal pain			
subjects affected / exposed	19 / 288 (6.60%)	11 / 137 (8.03%)	
occurrences (all)	30	17	
Abdominal pain upper			
subjects affected / exposed	18 / 288 (6.25%)	9 / 137 (6.57%)	
occurrences (all)	20	12	
Dyspepsia			
subjects affected / exposed	13 / 288 (4.51%)	9 / 137 (6.57%)	
occurrences (all)	15	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 288 (16.67%)	14 / 137 (10.22%)	
occurrences (all)	60	17	
Dyspnoea			

subjects affected / exposed	42 / 288 (14.58%)	17 / 137 (12.41%)	
occurrences (all)	52	27	
Pneumonitis			
subjects affected / exposed	19 / 288 (6.60%)	0 / 137 (0.00%)	
occurrences (all)	23	0	
Epistaxis			
subjects affected / exposed	14 / 288 (4.86%)	8 / 137 (5.84%)	
occurrences (all)	17	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	62 / 288 (21.53%)	16 / 137 (11.68%)	
occurrences (all)	74	21	
Skin hyperpigmentation			
subjects affected / exposed	32 / 288 (11.11%)	1 / 137 (0.73%)	
occurrences (all)	36	1	
Dry skin			
subjects affected / exposed	27 / 288 (9.38%)	8 / 137 (5.84%)	
occurrences (all)	27	8	
Rash			
subjects affected / exposed	17 / 288 (5.90%)	5 / 137 (3.65%)	
occurrences (all)	18	6	
Pruritus			
subjects affected / exposed	15 / 288 (5.21%)	2 / 137 (1.46%)	
occurrences (all)	16	2	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 288 (0.69%)	32 / 137 (23.36%)	
occurrences (all)	2	70	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 288 (7.99%)	6 / 137 (4.38%)	
occurrences (all)	24	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 288 (10.76%)	11 / 137 (8.03%)	
occurrences (all)	36	14	
Back pain			

subjects affected / exposed occurrences (all)	22 / 288 (7.64%) 23	11 / 137 (8.03%) 14	
Pain in extremity subjects affected / exposed occurrences (all)	18 / 288 (6.25%) 20	12 / 137 (8.76%) 19	
Myalgia subjects affected / exposed occurrences (all)	11 / 288 (3.82%) 14	7 / 137 (5.11%) 7	
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	25 / 288 (8.68%) 28	14 / 137 (10.22%) 14	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 288 (3.13%) 12	8 / 137 (5.84%) 11	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	61 / 288 (21.18%) 75	15 / 137 (10.95%) 20	
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 288 (3.82%) 13	9 / 137 (6.57%) 12	
Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 288 (2.43%) 7	7 / 137 (5.11%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2017	<p>This substantial amendment was prepared upon request of the regulatory authorities. The changes are summarized below:</p> <ul style="list-style-type: none">- Inclusion criterion 3 on previous HER2-targeting treatment has been specified in more detail.- Inclusion criterion 4 on HER2 status has been specified in more detail.- An exclusion criterion on prior pulmonary disease has been added as criterion 9.- Previous exclusion criterion 9 on HIV and hepatitis has been amended to allow the inclusion of HIV infected patients.- Two additional time points (Cycle 2 Day 1 and Cycle 4 Day 1) for assessments of the QoL questionnaires have been added to the flowchart.- The dose modification guidances for eye toxicity and pneumonitis have been adjusted.- The ECG assessments requirements for the physician's choice group receiving Lapatinib + Capecitabine have been explained in more detail.- In addition to Europe and North-America also sites in Singapore are planned to participate, this has been added.- Details regarding the required infusion materials have been replaced by more general wording with reference to the pharmacy manual in which full details are described.
09 November 2017	<p>This substantial amendment was prepared upon request of the regulatory authorities. The changes are summarized below:</p> <ul style="list-style-type: none">- The flowchart has been updated to add pregnancy tests on Day 1 of every cycle and at the treatment discontinuation visit.- The flowchart has been updated to add an ECG assessment at Cycle 3 Day 1.- A total of 5 protocol sections have been updated to re-iterate and emphasize the importance to follow the SmPC guidance for patient selection and management in the physician's choice group.- A section on the benefit/risk ratio has been added.- In relation to cardiotoxicity it has been added that clinically relevant electrolyte disturbances should be corrected.- The possibility to enable further SYD985 treatment when the study has ended is added.- The indicated contraception has been updated to be aligned with the CTFG recommendations.
11 September 2018	<p>This substantial amendment was prepared for the following reasons:</p> <ul style="list-style-type: none">- Section 9.5.1 has been updated to add the possibility to reduce dosing to 0.6 mg/kg which has been shown to be an effective and safe dose in the phase I study.- Section 11.9 and the flowchart have been updated to add the possibility for serum pregnancy test in addition to urine pregnancy test as routinely performed in several clinical sites.- Section 12.10, 14.7 and the synopsis have been updated to describe that the DMC will assess the assumptions underlying the sample size estimation.- Section 2 has been updated to reflect changes in the vendor responsibilities.

12 April 2019	<p>This substantial amendment was prepared for the following reasons:</p> <ul style="list-style-type: none"> - Upon request of the DMC Keratitis grade ≥ 2 has been added as an adverse event of special interest - In consultation with the Steering committee and the DMC Section 8.2 has been updated to add the possibility to allow re-screening for patients for whom during screening on the brain CT/MRI a previously unknown asymptomatic metastasis is observed. - Section 11.9 and the flowchart have been updated to add the possibility to perform the pregnancy test up to 3 days before Day 1 of a new cycle for practical reasons. - Section 11.21 and the flowchart have been updated to add that the treatment discontinuation visit should be performed before new anti-cancer treatment is initiated.
24 May 2019	<p>This substantial amendment was prepared upon request of the regulatory authorities. The changes are summarized below:</p> <ul style="list-style-type: none"> - Section 5.5.1 has been updated to include additional information on ILD/Pneumonitis. - Section 9.5.1.4 dose modifications for ILD/pneumonitis have been elaborated. - Section 11.5 oxygen saturation by pulse oximetry has been added to the vital signs assessments at all visits.
22 October 2019	<p>This substantial amendment has been prepared for the following reason:</p> <ul style="list-style-type: none"> - As part of their evaluation the independent DMC assessed the validity of the initial assumptions underlying the sample size estimation with regards to drop-out rates. Based on their pre-planned interim evaluation the independent DMC has recommended to adjust the sample size and enroll a total of 423 patients to ensure sufficient power for the primary endpoint analysis.
18 January 2021	<p>This substantial amendment has been prepared for the following reason:</p> <ul style="list-style-type: none"> - To include the possibility to analyse the primary endpoint of the trial when at least 95% of the patients have discontinued treatment. - Section 2 has been updated to reflect changes in the vendor responsibilities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported