Clinical trial results:
An Open-label, Multicenter Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym015, a Monoclonal Antibody Mixture Targeting MET, in Patients with Advanced Solid Tumor Malignancies

Summary

EudraCT number	2016-003912-11
Trial protocol	DK ES
Global end of trial date	17 December 2020

Results information

Result version number	v1 (current)
This version publication date	16 July 2022
First version publication date	16 July 2022
Summary attachment (see zip file)	CSR Synopsis and Conclusions (Symphogen-Sym015 CSR Synopsis and Conclusions.docx)

Trial information

Trial identification

Sponsor protocol code	Sym015-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02648724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Symphogen A/S
Sponsor organisation address	Pederstrupvej 93, Ballerup, Denmark,
Public contact	Ulla H Hansen, Symphogen A/S, +45 45265050, uhh@symphogen.com
Scientific contact	Ulla H Hansen, Symphogen A/S, +45 45265050, uhh@symphogen.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	07 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2020
Global end of trial reached?	Yes
Global end of trial date	17 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients with MET-amplified, KRAS WT solid tumor malignancies without available therapeutic options.

Protection of trial subjects:

After EOT, patients continued to be followed for safety until 1 month (30+7 days) after the last dose of Sym015, when the 1-Month Follow-up (1M FUP) Visit was completed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	57
EEA total number of subjects	13

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)	34
From 65 to 84 years	15

85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening assessment (D-14 to D-1) included demographics, medical history, tumour history, physical examination, urinalysis, disease assessment as mutation status, extent of disease, prior anti-cancer treatment, etc.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Dose-Escalation

Arm description:

Sym015 was tested in four dose titration cohorts. A substitute or an additional dose level could potentially be evaluated.

Arm type	Experimental
Investigational medicinal product name	Sym015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sym015 solution administered as IV infusion at dose levels of 6 mg/kg, 12 mg/kg, 18 mg/kg or 24 mg/kg

Arm title	Part 2: Dose-Expansion

Arm description:

Comprises 3 Cohorts:
- Basket Cohort [n=25]: Patients with KRAS proto-oncogene wild-type (KRAS WT) advanced solid tumor malignancies with MET-amplification received Sym015 at the recommended Phase 2 dose. Included in this group was a subset of patients who received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI).
- NSCLC MET- Amplified Cohort [n=8]: Patients with advanced NSCLC with MET-amplification were to receive Sym015 at the RP2D. Patients may have received prior therapy with METtargeting and/or EGFR-targeting agents.
- NSCLC METex14del Cohort [n=12]: Patients with advanced NSCLC with METex14del were to receive Sym015 at the RP2D. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

Arm type	Experimental
Investigational medicinal product name	Sym015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sym015 solution administered as IV infusion

Number of subjects in period 1	Part 1: Dose-Escalation	Part 2: Dose-Expansion
Started	12	45
Completed	0	0
Not completed	12	45
Consent withdrawn by subject	2	1
Physician decision	-	2
Death	-	3
Unknown	1	-
Transferred to named patient program	-	1
Progressive disease	9	37
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Dose-Escalation
Reporting group description:	
Sym015 was tested in four dose titration cohorts. A substitute or an additional dose level could potentially be evaluated.	
Reporting group title	Part 2: Dose-Expansion
Reporting group description:	
Comprises 3 Cohorts: - Basket Cohort [n=25]: Patients with KRAS proto-oncogene wild-type (KRAS WT) advanced solid tumor malignancies with MET-amplification received Sym015 at the recommended Phase 2 dose. Included in this group was a subset of patients who received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI). - NSCLC MET- Amplified Cohort [n=8]: Patients with advanced NSCLC with MET-amplification were to receive Sym015 at the RP2D. Patients may have received prior therapy with METtargeting and/or EGFR-targeting agents. - NSCLC METex14del Cohort [n=12]: Patients with advanced NSCLC with METex14del were to receive Sym015 at the RP2D. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.	

Reporting group values	Part 1: Dose-Escalation	Part 2: Dose-Expansion	Total
Number of subjects	12	45	57
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	28	34
From 65-84 years	6	9	15
85 years and over	0	8	8
Age continuous Units: years			
arithmetic mean	60.1	61.4	
standard deviation	± 11.10	± 12	-
Gender categorical Units: Subjects			
Female	7	18	25
Male	5	27	32
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	10	43	53
Race (NIH/OMB) Units: Subjects			
Asian	0	17	17
Black or African American	1	1	2

White	10	25	35
Unknown or Not Reported	1	1	2
More than one race	0	1	1
ECOG-PS			
ECOG-PS is the Eastern Cooperative Oncology Group performance status. It describes patient functioning level on a 5 graded scale; 0 indicates the highest level of functioning and 5 the lowest			
Units: Subjects			
zero (0)	4	7	11
one (1)	8	36	44
two (2)	0	2	2
Site of primary tumour Units: Subjects			
Breast	1	1	2
Colon	3	2	5
Genitourinary	2	3	5
Hepatic (including gallbladder)	0	1	1
Liver	0	3	3
Neck	1	0	1
Other locally advanced sites	1	4	5
Other metastatics sites	2	1	3
Pancreas	1	0	1
Respiratory	0	19	19
Skin/soft tissue	1	0	1
Gastrointestinal	0	11	11
Histopathologic diagnosis Units: Subjects			
Adenocarcinoma	7	40	47
Misisng	5	5	10
Anatmoic based cancer type Units: Subjects			
Adenocarcinoma of Parotid Gland	1	0	1
Adenocarcinoma of Thymus	1	0	1
BRCA (breast cancer gene)	1	1	2
CRC (colorectal cancer)	3	3	6
Cholangiocarcinoma	1	0	1
GC (gastric cancer)	0	13	13
GU (genitourinary cancer)	2	3	5
HCC (hepatocellular carcinoma)	0	2	2
HCC-MIXED	0	1	1
HCC-Neuroendocrine	0	1	1
Lung-Neurocrine	0	1	1
NSCLC (non-small-cell lung carcinoma)	0	18	18
NSCLC-Sq type	0	2	2
Nasopharyngeal carcinoma	1	0	1
Pancreatic cancer	1	0	1
SCC (squamous cell carcinoma) of skin/soft tissue	1	0	1
Previous debulking surgery Units: Subjects			
Yes	3	10	13
No	9	35	44

Number of sites with metastasis Units: Subjects			
zero (0)	0	0	0
one (1)	2	10	12
two (2)	1	12	13
three (3)	4	13	17
more than 3	5	10	15
Body weight Units: kg			
arithmetic mean	75.9	67.2	
standard deviation	± 16.56	± 12.65	-

End points

End points reporting groups

Reporting group title	Part 1: Dose-Escalation

Reporting group description:

Sym015 was tested in four dose titration cohorts. A substitute or an additional dose level could potentially be evaluated.

Reporting group title	Part 2: Dose-Expansion

Reporting group description:

Comprises 3 Cohorts:
- Basket Cohort [n=25]: Patients with KRAS proto-oncogene wild-type (KRAS WT) advanced solid tumor malignancies with MET-amplification received Sym015 at the recommended Phase 2 dose. Included in this group was a subset of patients who received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI).
- NSCLC MET- Amplified Cohort [n=8]: Patients with advanced NSCLC with MET-amplification were to receive Sym015 at the RP2D. Patients may have received prior therapy with METtargeting and/or EGFR-targeting agents.
- NSCLC METex14del Cohort [n=12]: Patients with advanced NSCLC with METex14del were to receive Sym015 at the RP2D. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

Subject analysis set title	Part 2: Basket Cohort
Subject analysis set type	Full analysis

Subject analysis set description:

Part 2: Basket Cohort - Patients with KRAS proto-oncogene wild-type (KRAS WT) advanced solid tumor malignancies with MET-amplification received Sym015 at the recommended Phase 2 dose. Included in this group was a subset of patients who received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI).

Subject analysis set title	Part 2: Patients in NSCLC MET-Amplified Cohort
Subject analysis set type	Full analysis

Subject analysis set description:

NSCLC MET- Amplified Cohort: Patients with advanced NSCLC with MET-amplification were to receive Sym015 at the RP2D. Patients may have received prior therapy with METtargeting and/or EGFRtargeting agents.

Subject analysis set title	Part 2: Patients in NSCLC METex14Del Cohorot
Subject analysis set type	Full analysis

Subject analysis set description:

Part2: NSCLC METex14del Cohort: Patients with advanced NSCLC with METex14del were to receive Sym015 at the RP2D. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents.

Subject analysis set title	Part 1: 6 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort of subjects receiving a dose of 6 mg/kg of Sym015 administered by intravenous infusion Q2W. Q2W = every second week

Subject analysis set title	Part 1: 12 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort of subjects receiving a dose of 12 mg/kg of Sym015 administered by intravenous infusion Q2W. Q2W = every second week

Subject analysis set title	Part 1: 18 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort of subjects receiving a dose of 18 mg/kg of Sym015 administered by intravenous infusion Q2W. Q2W = every second week

Subject analysis set title	Part 1: 24 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort of subjects receiving a dose of 24 mg/kg of Sym015 administered by intravenous infusion Q2W. Q2W = every second week

Subject analysis set title	Part 2: Basket Cohort, with prior MET-targeting TKI therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in Basket Cohort, with prior MET-targeting TKI therapy. MET = MET proto-oncogene tyrosine kinase, hepatocyte growth factor receptor. TKI = tyrosine kinase inhibitor.

Subject analysis set title	Part 2: Basket Cohort, without prior MET-targeting TKI therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in Basket Cohort, without prior MET-targeting TKI therapy. MET = MET proto-oncogene tyrosine kinase, hepatocyte growth factor receptor. TKI = tyrosine kinase inhibitor.

Primary: Primary Endpoint - Part 1

End point title	Primary Endpoint - Part 1[1][2]

End point description:

Occurrence of DLTs During Cycle 1 of Sym015 Administration:

The primary objective of Part 1 was to assess the safety and tolerability of Sym015 on a Q2W schedule. This was assessed by evaluating the occurrence of dose-limiting toxicities (DLTs) during Cycle 1 of Sym015 administration. Q2W = every second week.

End point type	Primary

End point timeframe:

Cycle 1, the initial 28-day period of Q2W dosing

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical analyses provided, as there were no occurrences recorded.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 1: Dose-Escalation			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of DLTs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Primary Endpoint - Part 2

End point title	Primary Endpoint - Part 2[3]

End point description:

Documented, Confirmed Objective Response (OR):

The primary objective of Part 2 was to evaluate the antitumor activity of Sym015 when administered at the Q2W RP2D to patients in the different cohorts. Documented OR was defined as a partial response [PR] or complete response [CR], as assessed by the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 at any time during trial participation by Investigator assessment.

Q2W - every second week; RP2D = recommended phase 2 dose

End point type	Primary

End point timeframe:

24 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Basket Cohort	Part 2: Patients in NSCLC MET-Amplified Cohort	Part 2: Patients in NSCLC METex14Del Cohorot	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	8	12	
Units: Documented, Confirmed Objective Response	0	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1

End point title	Secondary Endpoint - Part 1[4]

End point description:

Determine a Q2W RP2D of Sym015

Determination based on an evaluation of the patient data for DLTs from Part1. (Q2W = every second week, RP2D = recommended phase 2 dose).

End point type	Secondary

End point timeframe:

12 Months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 1: Dose-Escalation			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: mg/kg				
number (not applicable)				

Notes:

[5] - It was not possible to determine this endpoint as no DLTs were observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (immunogenicity)

End point title	Secondary Endpoint - Part 1 (immunogenicity)

End point description:

Immunogenicity of Sym015: Part 1
Serum sampling was done to assess the potential for anti-drug (ADA) formation

End point type	Secondary

End point timeframe:

Cycle 1: Day (D) 1
Cycle 3, 5, 7: D1 (+-2)
End of treatment: at or by D10
Follow-up: 1 month after the last dose of study treatment (30+7D)

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: Count of participants				
Cycle 1 - day 1 (not done)	0	0	0	0
Cycle 1 - day 1 (negative)	3	3	3	3
Cycle 1 - day 1 (patient withdrawn)	0	0	0	0
Cycle 3 - day 1 (not done)	0	0	0	0
Cycle 3 - day 1 (negative)	1	0	2	0
Cycle 3 - day 1 (patient withdrawn)	2	3	1	3
End of treatment (not done)	0	0	0	1
End of treatment (negative)	3	2	1	2
End of treatment (patient withdrawn)	0	1	2	0
1-month follow-up (not done)	0	1	0	0
1-month follow-up (negative)	2	1	0	2
1-month follow-up (patient withdrawn)	1	1	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (immunogenicity)

End point title	Secondary Endpoint - Part 2 (immunogenicity)

End point description:

Immunogenicity of Sym015: Part 2

Serum sampling was done to assess the potential for anti-drug antibody (ADA) formation

End point type	Secondary

End point timeframe:

Cycle 1: Day (D) 1
Cycle 2, 3, 5, 7: D1 (+-2)
End of treatment: At or by D10
Follow-up: 1 month after last does of study treatment (30+7D)

End point values	Part 2: Basket Cohort	Part 2: Patients in NSCLC MET-Amplified Cohort	Part 2: Patients in NSCLC METex14Del Cohorot	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24	8	12	
Units: Count of participants				
Cycle 1 - day 1 (not done)	0	0	0	
Cycle 1 - day 1 (negative)	25	8	12	
Cycle 1 - day 1 (positive)	0	0	0	
Cycle 1 - day 1 (patient withdrawn)	0	0	0	
Cycle 2 - day 1 (not done)	1	0	0	
Cycle 2 - day 1 (negative)	21	8	11	
Cycle 2 - day 1 (positive)	0	0	0	
Cycle 2 - day 1 (patient withdrawn)	3	0	1	
Cycle 3 - day 1 (not done)	1	1	0	
Cycle 3 - day 1 (negative)	8	7	8	
Cycle 3 - day 1 (positive)	0	0	0	
Cycle 3 - day 1 (patient withdrawn)	16	0	4	
Cycle 5 - day 1 (not done)	0	0	1	
Cycle 5 - day 1 (negative)	6	6	5	
Cycle 5 - day 1 (positive)	0	0	0	
Cycle 5 - day 1 (patient withdrawn)	19	2	6	
Cycle 7 - day 1 (not done)	0	1	0	
Cycle 7 - day 1 (negative)	2	2	5	
Cycle 7 - day 1 (positive)	0	0	0	
Cycle 7 - day 1 (patient withdrawn)	23	5	7	
End of treatment (not done)	5	0	0	
End of treatment (negative)	15	7	9	
End of treatment (positive)	1	0	0	
End of treatment (patient withdrawn)	4	1	3	
1-month follow up (not done)	0	1	1	
1-month follow up (negative)	10	3	5	
1-month follow up (positive)	1	0	0	
1-month follow up (patient withdrawn)	14	4	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (AUC)

End point title	Secondary Endpoint - Part 1 (AUC)

End point description:

Part 1: Area Under the Concentration-time Curve in a Dosing Interval (AUC) Following 1st Dose

Estimated using non-compartmental methods and actual time points following the first dose of Sym015.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. Samples taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: h * µg/mL				
median (full range (min-max))	17900 (17100 to 24500)	35700 (31600 to 42900)	82500 (75200 to 86200)	76800 (55200 to 86400)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (AUC)

End point title	Secondary Endpoint - Part 2 (AUC)[6]

End point description:

Part 2: Area Under the COncentration-time Curve in a Dosing Interval (AUC)

Estimated using non-compartmental methods and actual time points following the first dose of Sym015 for the whole basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after doing. Sample taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: h * µg/mL				
median (full range (min-max))	60500 (19900 to 95200)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (Cmax)

End point title	Secondary Endpoint - Part 1 (Cmax)

End point description:

Part 1: C max

Maximum serum concentration was derived from observed data.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. Samples were taken pre-dosing and at 1, 2, 4, 8, 24, and 48 hours after the end of infusion.

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: µg/mL				
median (full range (min-max))	146 (141 to 151)	286 (275 to 323)	563 (419 to 711)	561 (379 to 726)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (Cmax)

End point title	Secondary Endpoint - Part 2 (Cmax)[7]

End point description:

Part 2: C max

Maximum serum concentration was derived from observed data following the first dose of Sym015 for the full basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. Samples were taken pre-dosing, and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: µg/mL				
median (full range (min-max))	495 (312 to 1170)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (Tmax)

End point title	Secondary Endpoint - Part 1 (Tmax)

End point description:

Part 1: Time to Reach Maximum Concentration (Tmax)

Time to reach maximum concentration (Tmax) was derived from observed data.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. Samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: hours				
median (full range (min-max))	2.1 (2 to 5)	1.1 (1 to 2)	3.5 (3 to 4)	3.0 (3 to 9)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (Tmax)

End point title	Secondary Endpoint - Part 2 (Tmax)[8]

End point description:

Part 2: Time to Reach Maximum Concentration (Tmax)

Time to reach maximum concentration (Tmax) was derived from observed data following the first dose of Sym015 for the full basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: hours				
median (full range (min-max))	2.67 (1.42 to 44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (Ctrough)

End point title	Secondary Endpoint - Part 1 (Ctrough)

End point description:

Part 1: Trough Concentration (Ctrough)

Ctrough was derived from observed data.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: µg/mL				
median (full range (min-max))	23.1 (19.2 to 31.5)	61.3 (56.1 to 65)	130 (127 to 187)	92.4 (91.3 to 151)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (Ctrough)

End point title	Secondary Endpoint - Part 2 (Ctrough)[9]

End point description:

Part 2: Trough Concentration (Ctrough)

Ctrough was derived from observed data following the first dose of Sym015 for the whole basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: µg/mL				
median (full range (min-max))	92.4 (24.1 to 429)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (T½)

End point title	Secondary Endpoint - Part 1 (T½)

End point description:

Part 1: Elimination Half-life (T½)

Estimated using non-compartmental methods and actual time points.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	1	1
Units: hours				
median (full range (min-max))	179 (116 to 179)	137 (137 to 137)	193 (193 to 193)	170 (170 to 170)

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (T½)

End point title	Secondary Endpoint - Part 2 (T½)[10]

End point description:

Part 2: Elimination Half-life (T½)

Estimated using non-compartmental methods and actual time points following the first dose of Sym015 for the whole basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: hours				
median (full range (min-max))	167 (87.1 to 217)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 1 (CL)

End point title	Secondary Endpoint - Part 1 (CL)

End point description:

Part 1: Clearance (CL)

Estimated using non-compartmental methods and actual time points.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

End point values	Part 1: 6 mg/kg	Part 1: 12 mg/kg	Part 1: 18 mg/kg	Part 1: 24 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	0[11]	0[12]
Units: mL/h				
median (full range (min-max))	0.3 (0.3 to 0.3)	0.2 (0.2 to 0.2)	(to)	(to)

Notes:

[11] - None evaluated

[12] - None evaluated

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (CL)

End point title	Secondary Endpoint - Part 2 (CL)[13]

End point description:

Part 2: Clearance (CL)

Estimated using non-compartmental methods and actual time points following the first dose of Sym015 for the whole basket cohort.

End point type	Secondary

End point timeframe:

From time zero to 48 hours after dosing. The samples were taken pre-dosing and at 1, 2, 4, 8, 24 and 48 hours after end of infusion.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There were no statistical analyses for this endpoint

End point values	Part 2: Dose-Expansion			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mL/h				
median (full range (min-max))	0.327 (0.187 to 0.525)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (additional preliminary evaluation of antitumour activity, assessed by OR)

End point title	Secondary Endpoint - Part 2 (additional preliminary evaluation of antitumour activity, assessed by OR)

End point description:

Part 2: Additional Preliminary Evaluation of the Antitumor Activity of Sym015 When Administered at the Q2W RP2D in a Subset of Patients. Assessed by OR

This applies to the subset of patients in the Basket Cohort who received prior therapy with a MET-targeting TKI. Documented OR (defined as PR or CR), assessed by RECIST v1.1 at any time during trial participation by Investigator assessment.

Objective Response (OR) is presented. Documented OR was defined as partial response [PR] or complete response [CR]) as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 at any time during trial participation by Investigator assessment.

End point type	Secondary

End point timeframe:

24 months

End point values	Part 2: Basket Cohort, with prior MET-targeting TKI therapy	Part 2: Basket Cohort, without prior MET-targeting TKI therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	20		
Units: Count of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Part 2 (additional preliminary evaluation of antitumour activity, assessed by DCR

End point title	Secondary Endpoint - Part 2 (additional preliminary evaluation of antitumour activity, assessed by DCR

End point description:

Part 2: Additional Preliminary Evaluation of the Antitumor Activity of Sym015 When Administered at the Q2W RP2D in a Subset of Patients. Assessed by DCR.

This applies to the subset of patients in the Basket Cohort who received prior therapy with a MET-targeting TKI. Documented OR (defined as PR or CR), assessed by RECIST v1.1 at any time during trial participation by Investigator assessment.

Disease control rate (DCR) is presented. The DCR was defined as the percentage of patients who had BOR of confirmed CR or confirmed PR or SD (including unconfirmed CR/PR, provided 6 weeks minimum criteria for SD duration was met).
BOR = Best Overall Response. CR = Complete Response. PR = Partial Response. SD = Stable Disease.

End point type	Secondary

End point timeframe:

24 Months

End point values	Part 2: Basket Cohort, with prior MET-targeting TKI therapy	Part 2: Basket Cohort, without prior MET-targeting TKI therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	20		
Units: Count of participants	2	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Part 1: Dose-escalation

Reporting group description:

Sym015 was tested in four dose titration cohorts. A substitute or an additional dose level could potentially be evaluated.
Sym015: Sym015 is a mixture of two monoclonal antibodies which specifically bind to non-overlapping epitopes in the extracellular domain of MET.

Reporting group title	Part 2: Dose-Expansion

Reporting group description:

Basket Cohort:

Patients with KRAS proto-oncogene wild-type (KRAS WT) advanced solid tumor malignancies with MET-amplification received Sym015 at the recommended Phase 2 dose. Included in this group was a subset of patients who received prior therapy with a MET-targeting tyrosine kinase inhibitor (TKI).

Sym015: Sym015 is a mixture of two monoclonal antibodies which specifically bind to non-overlapping epitopes in the extracellular domain of MET.

NSCLC MET-Amplified Cohort:
Patients with advanced NSCLC with MET-amplification were to receive Sym015 at the RP2D. Patients may have received prior therapy with METtargeting and/or EGFR-targeting agents.

NSCLC METex14del Cohort:
Patients with advanced NSCLC with METex14del were to receive Sym015 at the RP2D. Tumors need not be MET-amplified, and patients may have received prior therapy with MET-targeting and/or EGFR-targeting agents. mutation.

Serious adverse events	Part 1: Dose-escalation	Part 2: Dose-Expansion	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	18 / 45 (40.00%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: Dose-escalation	Part 2: Dose-Expansion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	43 / 45 (95.56%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 12 (16.67%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	4	
Early satiety			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Facial pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	10 / 45 (22.22%)	
occurrences (all)	4	11	
Feeling abnormal			

subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	7 / 45 (15.56%)	
occurrences (all)	0	11	
Reproductive system and breast disorders			
Pelvic discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	8 / 45 (17.78%)	
occurrences (all)	1	11	
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	4 / 45 (8.89%)	
occurrences (all)	1	5	
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Respiratory tract congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	5 / 45 (11.11%)	
occurrences (all)	0	5	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 12 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	4	
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	5	
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 45 (4.44%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 12 (16.67%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	1 / 12 (8.33%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Somnolence			
subjects affected / exposed	2 / 12 (16.67%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 12 (0.00%)	8 / 45 (17.78%)	
occurrences (all)	0	13	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Ear haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	2 / 12 (16.67%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	7 / 45 (15.56%)	
occurrences (all)	0	8	
Ascites			
subjects affected / exposed	1 / 12 (8.33%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	2 / 12 (16.67%)	9 / 45 (20.00%)	
occurrences (all)	2	9	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	4 / 45 (8.89%)	
occurrences (all)	2	4	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	5 / 45 (11.11%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	10 / 45 (22.22%)	
occurrences (all)	1	10	
Presbyoesophagus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Salivary gland enlargement			

subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	4 / 45 (8.89%)	
occurrences (all)	3	4	
Oedema peripheral			
subjects affected / exposed	2 / 12 (16.67%)	10 / 45 (22.22%)	
occurrences (all)	4	18	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	4	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	6 / 45 (13.33%)	
occurrences (all)	0	6	
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 12 (25.00%)	9 / 45 (20.00%)	
occurrences (all)	3	10	
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			

subjects affected / exposed	2 / 12 (16.67%)	6 / 45 (13.33%)	
occurrences (all)	2	10	
Hypokalaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 45 (2.22%)	
occurrences (all)	3	4	
Hypomagnesaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2016	Summary of significant changes included the following: 1. Part 1 of the study was modified to make premedication mandatory prior to each dose of Sym015. Part 2 of the study was modified to make premedication mandatory prior to each dose of Sym015 during Cycle 1. 2. Definition of dose-limiting toxicities was modified. 3. Protocol was modified to discontinue therapy for all patients who met Hy's Law criteria that could not be explained by factors not related to Sym015. 4. Additional criteria included for dose reduction due to toxicity. 5. Allowed GnRH analogues in patients with prostate cancer.
22 February 2016	Summary of significant changes included the following: 1. Part 1 of the study was modified to make KRAS mutation testing mandatory to include only patients with KRAS WT solid tumor malignancies.
02 May 2016	Summary of significant changes included the following: 1. Inclusion criteria No. 6 was modified to require KRAS mutation testing according to institutional standards in order to utilize the various testing platforms that were available at the participating study sites. 2. Part 1 of the study was modified to include a tumor biopsy during screening for assessment of KRAS mutational status, if necessary, for eligibility assessment. 3. Part 2 of the study was modified to include an ADA sample time point at C2/D1. 4. It was clarified that AEs/SAEs were reported from signing of informed consent for participation in the study. Furthermore, it was clarified that patients who signed informed consent and were subsequently considered to be screening failures were followed for AEs/SAEs until it was determined that they were not to be participating in the study. 5. Reporting requirements for safety data to Sponsor or designee were explained. 6. It was made clear that the sample size considerations were based on a 2-stage design, not a 2-stage Minmax design

04 November 2016	Summary of significant changes included the following: 1. The overall study design was modified by moving the Q3W Cohort from Part 1 to Part 2 to ensure patients with MET-amplification were treated in this Cohort and thereby introducing a Q2W Basket Cohort as well as a Q3W Basket Cohort in Part 2. 2. Study objectives, study endpoints and patient numbers were updated according to the change in overall study design. 3. 6-12 patients were allowed to be included in the Q3W Basket Cohort. 4. The selection of the Q2W RP2D was confirmed as 18 mg/kg loading dose infused over 1.5 hours on C1/D1 followed by Q2W maintenance doses of 12 mg/kg infused over 1 hour beginning on C1/D15. 5. The select inclusion criterion was modified. 6. The select exclusion criterion was modified and/or deleted. 7. It was clarified that a study site may choose to pre-screen patients utilizing archival tumor tissue to confirm MET-amplification status and/or KRAS mutational status before entering patients into screening for the treatment portion of the study. 8. The infusion time of Sym015 was modified to 1.5 hour (+10 minutes) for doses ≥ 18 mg/kg 9. Preference was made clear for the eligibility assessment for MET-amplification be done using tissue from a tumor biopsy. 10. Skin biopsies were removed from Part 2 of the study. 11. Dose-delay criteria 4 was updated. 12. One of the dose-limiting toxicities (2) was clarified. 13. Dose-reduction criteria 2 and 5 was updated in accordance with dose-limiting toxicity criteria. 14. Overall survival (OS) status was updated in the continued follow-up after the 1M FUP Visit and adjusted the follow-up schedule to be every 2 months. 15. It was updated that PD was not to be captured as an AEs unless the nature of the PD was different than expected. 16. Timelines for reporting of SAE Follow-up information was updated. 17. It was updated that the sample size determination to be based on a Simon's Optimal 2-stage design.
11 May 2017	Summary of significant changes included the following: 1. Inclusion criterion #5 was modified to clarify that patients must have had recurrent and/or PD and were without other therapeutic options. 2. Inclusion criterion #7 was revised to allow local assessment of KRAS-mutation and MET-amplification based on a peripheral blood sample (liquid biopsy). 3. Inclusion and exclusion criteria were modified to allow a subset of patients pretreated with a MET-targeting TKI. 4. It was specified that patients included based on MET-amplification from a liquid biopsy were withdrawn if subsequent analysis of a tumor biopsy did not meet eligibility criteria, and the patients did not have clinical benefit from therapy. Such patients were replaced. 5. The option for investigators was added to include an H2 antagonist and/or acetaminophen premedication, where indicated. 6. Prohibited medication section was modified to allow steroid therapy as prophylaxis for contrast reactions. 7. Other minor updates and clarifications were included.

20 November 2017	Summary of significant changes included the following: 1. The overall study design was modified by removing Q3W dosing with Sym015, which was not to be evaluated, and a separate Cohort of KRAS WT, advanced NSCLC patients with METEx14 mutation was added. 2. Secondary study objectives were updated according to the change in overall study design. 3. The summary of clinical findings was updated based on the 7 MET-amplified patients that had been enrolled in the ongoing Part 2 Basket Cohort at the time of the amendment. 4. Inclusion and exclusion criteria were modified to allow enrolment of patients with NSCLC and other malignancies with METEx14 mutation, and who had been pre-treated with MET-targeting TKI. 5. Exclusion criteria was modified to specify time required between prior antineoplastic agent and C1/D1, and prior immunosuppressive or systemic hormonal therapy. 6. Prohibited medication was modified to specify when the use of steroid therapy was considered not allowed. 7. The order of collection of tumor biopsy and biomarker blood sample was specified if collected at the same time point. 8. Other minor updates and clarifications were included
07 December 2018	Summary of significant changes included the following: 1. Effective with this protocol amendment, accrual to the Basket Cohort was suspended. Emerging literature allowed for the identification of specific tumor types that were more likely to respond to Sym015 treatment (e.g., NSCLC). With this change, a new Cohort of NSCLC MET-amplified patients had been added to Part 2 of the study design, for a total of three Cohorts. 2. With the suspension of the Basket Cohort, NSCLC MET-amplified patients entered to the Basket Cohort were counted toward the NSCLC MET-Amplified Cohort; NSCLC METEx14Del patients entered to the Basket Cohort were counted toward the NSCLC METEx14Del Cohort; patients with both were counted as MET-Amplified. 3. Updated clinical experience information had been added to the scientific background. 4. According to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for testing of HER2 amplification, MET amplification was defined as positive with a MET/CEP7 ratio of > 2.2 (occasionally 2.0). Symphogen had opted to change the cut-off to > 3.0 based on emerging data that suggest higher degrees of MET-amplification were associated with higher degree of response. 5. It was specified that concomitant therapy with bisphosphonates and denosumab were allowed during the dosing portion of the study. 6. It was clarified that after the screening assessments, targeted physical examination may have been performed as indicated. 7. The number of PK time points was reduced for patients entered to the NSCLC Cohorts. 8. The mandatory post-dosing tumor biopsy scheduled to be performed at the EOC2 or upon disease progression was made optional. 9. It was clarified that all analyses were related to and used only in connection with the data collected in the present study as well as future development of Sym015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported