



Clinical trial results:

Open-label, Randomized, Controlled, Multicenter Phase II Trial Investigating 2 Sym004 Doses versus Investigator's Choice (Best Supportive Care, Capecitabine, 5-FU) in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies

Summary

EudraCT number	2013-003829-29
Trial protocol	DE IT BE AT HU ES PL
Global end of trial date	26 April 2017

Results information

Result version number	v1 (current)
This version publication date	26 April 2019
First version publication date	26 April 2019

Trial information

Trial identification

Sponsor protocol code	Sym004-05
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02083653
WHO universal trial number (UTN)	-
Other trial identifiers	Previous Protocol Code (Merck KGaA): EMR200637-002

Notes:

Sponsors

Sponsor organisation name	Symphogen A/S
Sponsor organisation address	Pederstrupvej 93, Ballerup, Denmark, 2750
Public contact	Chief Scientific Officer, Symphogen A/S, +45 88382600, info@symphogen.com
Scientific contact	Chief Scientific Officer, Symphogen A/S, +45 88382600, info@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	24 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 October 2016
Global end of trial reached?	Yes
Global end of trial date	26 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of two different weekly dosing regimens of Sym004 compared with Investigator's choice in terms of overall survival time in subjects with metastatic colorectal cancer (mCRC) and acquired resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs).

Protection of trial subjects:

Prophylactic and reactive treatment guidelines for skin management were implemented in this trial to reduce the incidence of severe rash. Based on data derived from randomized controlled trials using this approach (e.g., Skin Toxicity Evaluation Protocol with Panitumumab [STEPP] trial), it was anticipated that the incidence of Grade 3 rash would be reduced by these measures. Subjects receiving Sym004 were monitored weekly for hypomagnesemia, and intravenous replacement treatment was instituted twice weekly for Grade 3 and Grade 4 toxicity. Premedication to avoid or minimize infusion-related reactions (IRRs) to Sym004 was mandated during the treatment period. The subjects were monitored for at least 1 hour post-infusion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2014
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	Poland: 25
Country: Number of subjects enrolled	Spain: 73
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Russian Federation: 30
Worldwide total number of subjects	254
EEA total number of subjects	202

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)	145
From 65 to 84 years	105
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female, at least 18 years of age with histologically or cytologically confirmed mCRC, KRAS WT at initial diagnosis. Failure of or intolerance to 5-FU, Oxaliplatin, and Irinotecan. Acquired resistance to marketed anti-EGFR mAbs as defined in the protocol. Measurable disease defined as one or more target lesions according to RECIST.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Arm A: Sym004 (12 mg/kg)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sym004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Sym004 was administered as an intravenous infusion at a dose of 12 mg/kg weekly until unacceptable toxicity, disease progression, or consent withdrawal. The first administration of Sym004 was performed on the same day as randomization or no later than 72 hours after randomization.

Arm title	Arm B: Sym004 (9/6 mg/kg)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sym004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Sym004 was administered as an intravenous infusion at a loading dose of 9 mg/kg followed by 6 mg/kg weekly until unacceptable toxicity, disease progression, or consent withdrawal. The first administration of Sym004 was performed on the same day as randomization or no later than 72 hours after randomization.

Arm title	Arm C: Investigator's Choice
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Arm description:

Best supportive care (BSC) or Fluorouracil (5-FU, Adrucil) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.

Arm type	Active Comparator or BSC
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No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice
Started	83	86	85
Completed	83	86	85

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Sym004 (12 mg/kg)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sym004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Sym004 was administered as an intravenous infusion at a dose of 12 mg/kg weekly until unacceptable toxicity, disease progression, or consent withdrawal. The first administration of Sym004 was performed on the same day as randomization or no later than 72 hours after randomization.

Arm title	Arm B: Sym004 (9/6 mg/kg)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sym004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Sym004 was administered as an intravenous infusion at a loading dose of 9 mg/kg followed by 6 mg/kg weekly until unacceptable toxicity, disease progression, or consent withdrawal. The first administration of Sym004 was performed on the same day as randomization or no later than 72 hours after randomization.

Arm title	Arm C: Investigator's Choice
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Arm description:

Best supportive care (BSC) or Fluorouracil (5-FU, Aducril) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per

Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.

Arm type	Active Comparator or BSC
No investigational medicinal product assigned in this arm	

Number of subjects in period 2^[1]	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice
Started	83	84	78
Completed	1	1	1
Not completed	82	83	77
Consent withdrawn by subject	2	1	2
Other Events	-	2	2
Adverse event, non-fatal	12	5	4
Death	2	2	2
Lost to follow-up	1	-	-
Progressive disease	65	73	63
Reason missing	-	-	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification:

In Arm A, all randomized subjects (83) were treated.

In Arm B, 86 subjects were randomized, but only 84 subjects were treated.

In Arm C, 85 subjects were randomized, but only 78 subjects were treated.

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Sym004 (12 mg/kg)
Reporting group description: -	
Reporting group title	Arm B: Sym004 (9/6 mg/kg)
Reporting group description: -	
Reporting group title	Arm C: Investigator's Choice
Reporting group description:	
Best supportive care (BSC) or Fluorouracil (5-FU, Adrucil) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.	

Reporting group values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice
Number of subjects	83	86	85
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age is relative to time of informed consent for this trial. Age was omitted for privacy reasons for 5 subjects in Germany. In the Subjects Enrolled per Age Group, a mean age of 63 years was used for the 5 German subjects.			
Units: years			
arithmetic mean	62.2	64.2	61.4
standard deviation	± 9.91	± 10.41	± 10.70
Gender categorical			
Units: Subjects			
Female	31	32	31
Male	52	54	54
Ethnicity			
Ethnicity is presented as 'Not Reported' for subjects living in France.			
Units: Subjects			
Hispanic or Latino	5	5	5
Not Hispanic or Latino	69	72	70
Unknown or not reported	9	9	10
Race			
Race is presented as 'Not Reported' for subjects living in France.			
Units: Subjects			

American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	0
White	72	75	73
More than one race	0	0	0
Unknown or Not Reported	9	9	12
Region of Enrollment			
Units: Subjects			
Austria	0	1	1
Belgium	3	6	5
Hungary	0	1	5
United States	8	6	8
Poland	10	8	7
Italy	17	12	20
France	9	9	10
Germany	4	0	1
Russia	8	12	10
Spain	24	31	18
Height			
Units: centimeters (cm)			
arithmetic mean	168.9	169.1	167.9
standard deviation	± 10.82	± 9.71	± 9.56
Weight			
Units: kilograms (kg)			
arithmetic mean	75.3	74.0	76.0
standard deviation	± 13.51	± 14.14	± 16.13
Body Mass Index (BMI)			
Units: kg/m ²			
arithmetic mean	26.5	25.8	26.8
standard deviation	± 4.43	± 4.26	± 4.59

Reporting group values	Total		
Number of subjects	254		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Age is relative to time of informed consent for this trial. Age was omitted for privacy reasons for 5 subjects in Germany. In the Subjects Enrolled per Age Group, a mean age of 63 years was used for the 5 German subjects.			
Units: years			

arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	94		
Male	160		
Ethnicity			
Ethnicity is presented as 'Not Reported' for subjects living in France.			
Units: Subjects			
Hispanic or Latino	15		
Not Hispanic or Latino	211		
Unknown or not reported	28		
Race			
Race is presented as 'Not Reported' for subjects living in France.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	220		
More than one race	0		
Unknown or Not Reported	30		
Region of Enrollment			
Units: Subjects			
Austria	2		
Belgium	14		
Hungary	6		
United States	22		
Poland	25		
Italy	49		
France	28		
Germany	5		
Russia	30		
Spain	73		
Height			
Units: centimeters (cm)			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilograms (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Units: kg/m ²			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Arm A: Sym004 (12 mg/kg)
Reporting group description: -	
Reporting group title	Arm B: Sym004 (9/6 mg/kg)
Reporting group description: -	
Reporting group title	Arm C: Investigator's Choice
Reporting group description:	Best supportive care (BSC) or Fluorouracil (5-FU, Adrucil) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.
Reporting group title	Arm A: Sym004 (12 mg/kg)
Reporting group description: -	
Reporting group title	Arm B: Sym004 (9/6 mg/kg)
Reporting group description: -	
Reporting group title	Arm C: Investigator's Choice
Reporting group description:	Best supportive care (BSC) or Fluorouracil (5-FU, Adrucil) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.

Primary: Overall Survival (OS) Time

End point title	Overall Survival (OS) Time
End point description:	OS based on product-limit (Kaplan-Meier) estimates. Confidence intervals for the median are calculated according to Brookmeyer and Crowley. If a subject had not died, survival time was censored at the last date the subject was known to be alive. The analysis population was the intent-to-treat (ITT) subpopulation, which includes all subjects who were randomized to investigational medicinal product (IMP). Analyses performed on the ITT analysis set will take into account subjects' allocation to treatment groups as randomized and not as treated.
End point type	Primary
End point timeframe:	From randomization until the date of death (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	86	85	
Units: Months				
median (confidence interval 95%)	7.9 (6.5 to 9.9)	10.3 (9.0 to 12.9)	9.6 (8.3 to 12.2)	

Statistical analyses

Statistical analysis title	Hazard ratio for Arm A vs. Arm C
Statistical analysis description: A Hazard ratio < 1 favors the Sym004 arm.	
Comparison groups	Arm A: Sym004 (12 mg/kg) v Arm C: Investigator's Choice
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.137
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.87

Statistical analysis title	Hazard ratio for Arm B vs. Arm C
Statistical analysis description: A Hazard ratio < 1 favors the Sym004 arm.	
Comparison groups	Arm B: Sym004 (9/6 mg/kg) v Arm C: Investigator's Choice
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.882
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.4

Secondary: Best Overall Response (OR) According to the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Best Overall Response (OR) According to the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1)
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End point description:

Tumor assessments were done via CT or magnetic resonance imaging (MRI) scans and evaluated per RECIST v1.1. The assessment for measurable disease during screening (within 14 days prior to Day 1) acts as the baseline assessment. Best OR was summarized for each treatment group by means of counts and percentages for the following categories: Complete Response (CR: disappearance of all target lesions), Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions), Progressive Disease (PD: at least a 20% increase in the sum of diameters of target lesions), Stable Disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) or Not Evaluable (NE).

The analysis population was the ITT subpopulation, which includes all subjects who were randomized to IMP. Analyses performed on the ITT analysis set will take into account subjects allocation to treatment group as randomized and not as treated.

End point type	Secondary
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End point timeframe:

From randomization until first radiological confirmed or clinical progression event, or death due to any cause, within 12 weeks after last tumor assessment (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	86	85	
Units: Participants				
Complete Response (CR)	0	0	1	
Partial Response (PR)	11	8	1	
Stable Disease (SD)	40	47	37	
Progressive Disease (PD)	27	28	31	
Not Evaluable (NE)	5	3	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Time

End point title	Progression Free Survival (PFS) Time
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End point description:

PFS based on product-limit (Kaplan-Meier) estimates. Confidence intervals for the median are calculated according to Brookmeyer and Crowley. Death will only be considered as an event if it occurs within 12 weeks after last tumor response assessment without progression.

The analysis population was the ITT subpopulation, which includes all subjects who were randomized to IMP. Analyses performed on the ITT analysis set will take into account subjects' allocation to treatment groups as randomized and not as treated.

End point type	Secondary
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End point timeframe:

From randomization until first event, where an event can be a progression (radiological confirmed or clinical progression) or death due to any cause (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	86	85	
Units: Months				
median (confidence interval 95%)	2.8 (1.8 to 3.2)	2.7 (2.6 to 3.3)	2.6 (1.4 to 3.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)
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End point description:

TTF based on product-limit (Kaplan-Meier) estimates. Confidence intervals for the median are calculated according to Brookmeyer and Crowley.

The analysis population was the ITT subpopulation, which includes all subjects who were randomized to IMP. Analyses performed on the ITT analysis set will take into account subjects' allocation to treatment groups as randomized and not as treated. Subjects who were randomized but not treated have been censored at the date of randomization.

End point type	Secondary
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End point timeframe:

From randomization until treatment discontinuation for any reason, including disease progression or death (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	86	85	
Units: Months				
median (confidence interval 95%)	2.1 (1.4 to 2.7)	2.6 (2.2 to 2.6)	1.6 (1.2 to 2.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence and Nature of Adverse Events (AEs), as Assessed by the Common Terminology Criteria for AEs (Version 4.03) (CTCAE v4.03).

End point title	Occurrence and Nature of Adverse Events (AEs), as Assessed by the Common Terminology Criteria for AEs (Version 4.03) (CTCAE v4.03).
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End point description:

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. The incidence and type of AEs (i.e., serious AE [SAE], treatment-emergent AE [TEAE]) were summarized by dose cohort according to MedDRA system organ classes and preferred terms. An AE was considered as treatment-emergent if it occurred during or after the first IMP administration. An AE that occurred before the first IMP administration and worsened thereafter was also considered an AE. Worsening was

reported as a new AE.

The analysis population was the safety analysis subpopulation, which includes all subjects who were administered any dose of IMP, and in addition those subjects in Arm C for which the intended control treatment is BSC. Subjects will be analyzed as treated and not as randomized.

End point type	Secondary
End point timeframe:	
From Baseline up to 28 days after the last IMP administration.	

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	84	78	
Units: Participants				
At least one TEAE	83	84	67	
At least one Serious TEAE	27	23	12	
TEAE leading to dose reduction	29	17	8	
TEAE leading to interruption of trial treatment	58	47	10	
TEAE leading to trial treatment withdrawal	12	5	6	
TEAE related to trial treatment	81	80	46	
TEAE, Grade ≥ 3	67	53	25	
Dermatologic toxicity	78	78	8	
Infusion-related reaction	27	26	0	
TEAE resulting in death	4	4	3	
Related Serious TEAE	9	6	2	
Related TEAE leading to dose reduction	29	17	6	
Related TEAE leading to interruption of treatment	53	42	7	
Related TEAE leading to treatment withdrawal	9	2	3	
Related TEAE, Grade ≥ 3	58	41	9	
Related TEAE resulting in death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Dose Intensity of Sym004

End point title	Relative Dose Intensity of Sym004
End point description:	
Treatment duration (weeks) is calculated as [(last dose date of Sym004 - first dose date of Sym004)+7] / 7 days.	
Sym004 dose received (mg/kg) is calculated as (total dose administered (mg)/weight (kg)).	
Dose Intensity is calculated as (cumulative Sym004 dose (mg/kg) / treatment duration (weeks)).	
Relative Dose Intensity is calculated as (dose intensity / planned dose intensity at randomization)*100.	
Percentages are based on the number of subjects in the safety analysis set.	
The analysis population was the safety analysis subpopulation, which includes all subjects who were administered any dose of IMP. Subjects will be analyzed as treated and not as randomized.	
End point type	Secondary

End point timeframe:

From first dose of study drug until disease progression (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	84		
Units: Percentage of relative dose intensity				
arithmetic mean (standard deviation)	80.49 (± 20.020)	88.91 (± 13.843)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Sym004 Concentrations

End point title	Pharmacokinetic (PK) Parameters: Sym004 Concentrations
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End point description:

The Sym004 serum concentration used for the PK evaluation was calculated as the sum of the serum concentrations of the 2 component monoclonal antibodies of Sym004, futuximab and modotuximab. Trough Concentration (C_{trough}) is equivalent to the concentration collected at the pre-dose timepoint. Maximum Concentration (C_{max}) is equivalent to the concentration collected at the end of infusion (EOI) timepoint.

The analysis population was the PK analysis set. Bioanalysis for serum concentration was done for a subset of subjects (N=19) at all scheduled timepoints; it was carried out only at Weeks 3, 5, 7 and the End of Treatment visit (EOT) for all other subjects. Additionally, the Week 1 Day 1 EOI concentration for Subject 2740012 was assessed.

End point type	Secondary
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End point timeframe:

Weeks 3, 5, and 7 and at the EOT visit, including a Week 1 and Week 2 subset.

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80 ^[1]	83 ^[2]		
Units: ug/ml				
arithmetic mean (standard deviation)				
Screening (Pre-dose)	0.50 (± 0.0)	0.50 (± 0.0)		
Week 1 Day 1 (Pre-dose)	0.50 (± 0.0)	0.75 (± 0.700)		
Week 1 Day 1 (EOI)	182.95 (± 97.686)	174.44 (± 47.023)		
Week 1 Day 1 (0.5 hours after EOI)	214.98 (± 46.242)	184.84 (± 33.103)		
Week 1 Day 1 (1 hours after EOI)	209.80 (± 60.707)	189.24 (± 38.923)		

Week 1 Day 1 (2 hours after EOI)	197.31 (± 65.801)	181.68 (± 37.577)		
Week 1 Day 1 (4 hours after EOI)	188.75 (± 68.421)	171.63 (± 35.862)		
Week 2 Day 1 (Pre-dose)	45.37 (± 28.604)	38.76 (± 10.311)		
Week 2 Day 1 (EOI)	275.42 (± 80.975)	145.91 (± 47.950)		
Week 3 Day 1 (Pre-dose)	92.66 (± 38.443)	44.26 (± 20.995)		
Week 3 Day 1 (EOI)	323.35 (± 83.412)	170.18 (± 50.323)		
Week 5 Day 1 (Pre-dose)	125.73 (± 61.644)	49.26 (± 30.252)		
Week 5 Day 1 (EOI)	354.91 (± 108.263)	168.94 (± 67.901)		
Week 7 Day 1 (Pre-dose)	128.30 (± 77.437)	58.38 (± 47.505)		
Week 7 Day 1 (EOI)	346.83 (± 136.083)	163.11 (± 74.967)		
End of Treatment	64.55 (± 79.250)	17.61 (± 24.474)		

Notes:

[1] - Overall number of subjects analyzed was 80. The number of subjects analyzed varied per timepoint.

[2] - Overall number of subjects analyzed was 83. The number of subjects analyzed varied per timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Time of Maximum Plasma Concentration (Tmax)

End point title	Pharmacokinetic (PK) Parameters: Time of Maximum Plasma Concentration (Tmax)
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End point description:

Tmax was defined as the time the PK sample was taken at end of infusion (EOI) relative to the start time of infusion (i.e., time between the start of infusion and the time of the EOI sample). For presentation of individual PK parameters and calculation of mean parameters, half of the lower limit of quantitation (LLOQ) value was used for concentration values below the LLOQ. The Sym004 serum concentration used for the PK evaluation was calculated as the sum of the serum concentrations of the 2 component monoclonal antibodies of Sym004 (futuximab and modotuximab).

The analysis population was the PK analysis set, defined as subjects having at least 1 Sym004 serum concentration above the LLOQ. Exposure to Sym004 was confirmed in the majority of subjects treated with Sym004 for at least 1 timepoint post-dose.

End point type	Secondary
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End point timeframe:

Day 1 on Weeks 1-3 followed by Week 5 Day 1 and Week 7 Day 1.

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80 ^[3]	83 ^[4]		
Units: Hours				
arithmetic mean (standard deviation)				

Week 1 Day 1	3.14 (± 0.822)	2.79 (± 0.210)		
Week 2 Day 1	2.82 (± 0.306)	2.33 (± 0.459)		
Week 3 Day 1	3.01 (± 0.555)	2.34 (± 0.477)		
Week 5 Day 1	2.74 (± 0.532)	2.06 (± 0.448)		
Week 7 Day 1	2.83 (± 0.867)	2.06 (± 0.473)		

Notes:

[3] - Overall number of subjects analyzed was 80. The number of subjects analyzed varied per visit.

[4] - Overall number of subjects analyzed was 83. The number of subjects analyzed varied per visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Host Immune Response: Number of Subjects With Anti-drug Antibodies (ADAs) to Sym004 Over Time

End point title	Host Immune Response: Number of Subjects With Anti-drug Antibodies (ADAs) to Sym004 Over Time
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End point description:

A validated double antigen bridging ELISA was used for screening, confirmation, and titration of patient samples for anti-Sym004 ADA. Using rabbit anti-Sym004 as an ADA control antibody, the lower limit of detection was 54 ng/mL in the absence of Sym004 and 500 ng/mL in the presence of Sym004 at 5 µg/mL. The timepoints for ADA sampling were chosen by the original sponsor for this trial. After the trial was transferred to Symphogen A/S, it was determined that not all samples were necessary for analysis. This is why the collection time points specified in the timeframe do not match with the data table. The analysis population was the safety analysis subpopulation, which includes all subjects who were administered any dose of IMP. Subjects will be analyzed as treated and not as randomized.

End point type	Secondary
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End point timeframe:

Every two weeks (Days 15, 29, and 43) followed by every six weeks thereafter (Days 78, 120, 162, etc.) until the End of Treatment Visit

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	84		
Units: Participants				
Screening, Negative	78	81		
Screening, Positive	2	0		
Screening, Not Reportable	1	0		
Screening, Missing	2	3		
Week 5 Day 1, Negative	59	62		
Week 5 Day 1, Positive	0	0		
Week 5 Day 1, Not Reportable	0	0		
Week 5 Day 1, Missing	24	22		
Week 12, Negative	24	35		
Week 12, Positive	0	0		
Week 12, Not Reportable	0	0		
Week 12, Missing	59	49		
Week 13, Negative	1	1		
Week 13, Positive	0	0		
Week 13, Not Reportable	0	0		

Week 13, Missing	82	83		
Week 24, Negative	0	1		
Week 24, Positive	0	0		
Week 24, Not Reportable	0	0		
Week 24, Missing	83	83		
End of Treatment Visit, Negative	60	55		
End of Treatment Visit, Positive	0	0		
End of Treatment Visit, Not Reportable	0	0		
End of Treatment Visit, Missing	23	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Assessed by the EORTC QLQ-C30 (Version 3)

End point title	Quality of Life Assessed by the EORTC QLQ-C30 (Version 3)
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End point description:

Scale: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (Version 3) [QLQ-C30, Version 3].

The QLQ-C30 is a 30-question scale used to assess cancer patients' quality of life based on 15 factors (e.g., global health status, physical functioning, role functioning, etc.). The scale is composed of both multi-item scales and single item measures. All of the scales and single-item measures range in score from 0 to 100:

- A high score for a functional scale represents a healthy level of functioning.
- A high score for the global health status represents a high quality of life.
- A high score for a symptom scale/item represents a high level of symptomatology (problems).

This measure was self-reported. Numbers analyzed between Week 1 and Week 7 differ from each other, as well from the overall number of subjects analyzed. Data could not be collected from subjects not compliant with reporting or once discontinued.

End point type	Secondary
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End point timeframe:

Assessed every 6 weeks (week 1 and week 7 reported)

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83 ^[5]	86 ^[6]	85 ^[7]	
Units: score on a scale				
arithmetic mean (full range (min-max))				
Global Health Status (Week 1 Day 1)	55.5 (0 to 92)	59.7 (8 to 100)	55.8 (8 to 100)	
Global Health Status (Week 7 Day 1)	57.4 (25 to 100)	59.4 (17 to 100)	59.7 (17 to 100)	
Physical Functioning (Week 1 Day 1)	76.4 (7 to 100)	78.7 (27 to 100)	77.7 (27 to 100)	
Physical Functioning (Week 7 Day 1)	82.1 (13 to 100)	83.0 (47 to 100)	76.7 (40 to 100)	
Role Functioning (Week 1 Day 1)	75.0 (0 to 100)	76.4 (0 to 100)	72.5 (0 to 100)	
Role Functioning (Week 7 Day 1)	81.1 (33 to 100)	82.4 (50 to 100)	72.8 (17 to 100)	

Emotional Functioning (Week 1 Day 1)	76.6 (17 to 100)	77.8 (17 to 100)	73.2 (0 to 100)
Emotional Functioning (Week 7 Day 1)	74.8 (0 to 100)	82.7 (33 to 100)	75.3 (17 to 100)
Cognitive Functioning (Week 1 Day 1)	87.4 (33 to 100)	86.2 (17 to 100)	87.5 (50 to 100)
Cognitive Functioning (Week 7 Day 1)	88.1 (33 to 100)	88.5 (33 to 100)	87.0 (33 to 100)
Social Functioning (Week 1 Day 1)	78.2 (17 to 100)	80.2 (17 to 100)	75.4 (17 to 100)
Social Functioning (Week 7 Day 1)	77.9 (0 to 100)	83.4 (50 to 100)	72.7 (0 to 100)
Fatigue Symptoms (Week 1 Day 1)	35.3 (0 to 89)	32.2 (0 to 100)	34.7 (0 to 100)
Fatigue Symptoms (Week 7 Day 1)	26.3 (0 to 78)	25.3 (0 to 78)	33.2 (0 to 78)
Nausea & Vomiting Symptoms (Week 1 Day 1)	7.9 (0 to 67)	6.4 (0 to 100)	7.8 (0 to 83)
Nausea & Vomiting Symptoms (Week 7 Day 1)	5.6 (0 to 33)	5.1 (0 to 50)	8.4 (0 to 50)
Pain Symptoms (Week 1 Day 1)	27.2 (0 to 100)	23.6 (0 to 100)	27.8 (0 to 100)
Pain Symptoms (Week 7 Day 1)	12.7 (0 to 50)	14.6 (0 to 67)	24.1 (0 to 83)
Dyspnoea Symptoms (Week 1 Day 1)	15.9 (0 to 100)	17.2 (0 to 100)	16.4 (0 to 100)
Dyspnoea Symptoms (Week 7 Day 1)	10.4 (0 to 67)	8.8 (0 to 100)	15.7 (0 to 100)
Insomnia Symptoms (Week 1 Day 1)	29.3 (0 to 100)	19.1 (0 to 100)	21.7 (0 to 100)
Insomnia Symptoms (Week 7 Day 1)	27.4 (0 to 100)	16.9 (0 to 100)	16.6 (0 to 67)
Appetite Loss Symptoms (Week 1 Day 1)	22.3 (0 to 100)	17.6 (0 to 100)	22.2 (0 to 100)
Appetite Loss Symptoms (Week 7 Day 1)	16.9 (0 to 100)	17.5 (0 to 67)	23.0 (0 to 100)
Constipation Symptoms (Week 1 Day 1)	15.0 (0 to 67)	16.0 (0 to 100)	11.4 (0 to 100)
Constipation Symptoms (Week 7 Day 1)	11.5 (0 to 67)	8.3 (0 to 67)	11.1 (0 to 67)
Diarrhoea Symptoms (Week 1 Day 1)	12.5 (0 to 100)	8.5 (0 to 100)	15.9 (0 to 100)
Diarrhoea Symptoms (Week 7 Day 1)	8.8 (0 to 100)	11.1 (0 to 67)	11.0 (0 to 67)
Financial Difficulties (Week 1 Day 1)	19.7 (0 to 67)	16.6 (0 to 100)	23.3 (0 to 100)
Financial Difficulties (Week 7 Day 1)	19.4 (0 to 100)	15.2 (0 to 67)	19.3 (0 to 100)

Notes:

[5] - Overall number of subjects analyzed was 83. Number of subjects analyzed varied per visit.

[6] - Overall number of subjects analyzed was 86. Number of subjects analyzed varied per visit.

[7] - Overall number of subjects analyzed was 85. Number of subjects analyzed varied per visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Assessed by the EORTC QLQ-CR29

End point title	Quality of Life Assessed by the EORTC QLQ-CR29
End point description:	
<p>Scale: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Colorectal Cancer Module (QLQ-CR29).</p> <p>The QLQ-CR29 is a 29-question scale used to assess colorectal cancer patients' quality of life based on 22 factors (e.g., body image, anxiety, weight, etc.). The scale is composed of both multi-item scales and single-item measures. All of the scales and single-item measures range in score from 0 to 100:</p> <ul style="list-style-type: none"> • A high score for a functional scale/item represents an unhealthy level of functioning, with the exception of one (1) scale pertaining to sexual interest (separated by sex). • A high score for a symptom scale/item represents a high level of symptomatology (problems). <p>This measure was self-reported. Numbers analyzed between Week 1 and Week 7 differ from each other, as well from the overall number of subjects analyzed. Data could not be collected from subjects not compliant with reporting or once discontinued.</p>	
End point type	Secondary

End point timeframe:

Assessed every 6 weeks (week 1 and week 7 reported)

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83 ^[8]	86 ^[9]	85 ^[10]	
Units: score on a scale				
arithmetic mean (full range (min-max))				
Body Image (Week 1 Day 1)	76.2 (0 to 100)	80.1 (1 to 100)	75.8 (0 to 100)	
Body Image (Week 7 Day 1)	76.4 (11 to 100)	77.6 (33 to 100)	78.2 (0 to 100)	
Anxiety (Week 1 Day 1)	50.0 (0 to 100)	48.2 (0 to 100)	43.0 (0 to 100)	
Anxiety (Week 7 Day 1)	57.1 (0 to 100)	61.1 (0 to 100)	50.9 (0 to 100)	
Weight (Week 1 Day 1)	79.5 (0 to 100)	85.6 (0 to 100)	78.3 (0 to 100)	
Weight (Week 7 Day 1)	86.6 (33 to 100)	89.6 (33 to 100)	88.0 (0 to 100)	
Sexual Function (Men) (Week 1 Day 1)	31.7 (0 to 100)	21.2 (0 to 100)	23.5 (0 to 100)	
Sexual Function (Men) (Week 7 Day 1)	33.2 (0 to 100)	26.6 (0 to 67)	34.9 (0 to 100)	
Sexual Function (Women) (Week 1 Day 1)	16.5 (0 to 33)	12.3 (0 to 67)	10.1 (0 to 67)	
Sexual Function (Women) (Week 7 Day 1)	16.6 (0 to 67)	13.6 (0 to 67)	11.0 (0 to 33)	
Urinary Frequency (Week 1 Day 1)	34.4 (0 to 100)	30.3 (0 to 83)	32.6 (0 to 100)	
Urinary Frequency (Week 7 Day 1)	28.2 (0 to 100)	28.8 (0 to 67)	18.5 (0 to 67)	
Blood and Mucus (Week 1 Day 1)	4.1 (0 to 50)	1.5 (0 to 33)	2.0 (0 to 33)	
Blood and Mucus (Week 7 Day 1)	2.6 (0 to 33)	3.1 (0 to 67)	2.3 (0 to 33)	
Stool Frequency (Week 1 Day 1)	15.5 (0 to 100)	11.3 (0 to 100)	14.1 (0 to 83)	
Stool Frequency (Week 7 Day 1)	13.4 (0 to 50)	11.8 (0 to 83)	13.1 (0 to 67)	
Urinary Incontinence (Week 1 Day 1)	8.2 (0 to 100)	7.5 (0 to 100)	7.4 (0 to 100)	
Urinary Incontinence (Week 7 Day 1)	7.0 (0 to 67)	4.8 (0 to 67)	1.9 (0 to 33)	
Dysuria (Week 1 Day 1)	4.0 (0 to 33)	2.9 (0 to 67)	3.0 (0 to 67)	
Dysuria (Week 7 Day 1)	3.2 (0 to 33)	2.1 (0 to 33)	0.9 (0 to 33)	
Abdominal Pain (Week 1 Day 1)	18.8 (0 to 100)	12.8 (0 to 100)	23.0 (0 to 100)	
Abdominal Pain (Week 7 Day 1)	10.4 (0 to 67)	10.8 (0 to 67)	16.6 (0 to 67)	
Buttock Pain (Week 1 Day 1)	11.6 (0 to 100)	10.8 (0 to 100)	9.9 (0 to 100)	
Buttock Pain (Week 7 Day 1)	4.4 (0 to 33)	8.8 (0 to 67)	7.4 (0 to 67)	
Bloated Feeling (Week 1 Day 1)	20.4 (0 to 100)	14.8 (0 to 67)	21.7 (0 to 100)	
Bloated Feeling (Week 7 Day 1)	13.3 (0 to 67)	12.1 (0 to 33)	12.9 (0 to 67)	
Dry Mouth (Week 1 Day 1)	25.1 (0 to 100)	17.0 (0 to 67)	22.1 (0 to 100)	
Dry Mouth (Week 7 Day 1)	26.8 (0 to 100)	29.2 (0 to 100)	13.8 (0 to 67)	
Hair Loss (Week 1 Day 1)	17.1 (0 to 100)	11.1 (0 to 100)	14.6 (0 to 100)	
Hair Loss (Week 7 Day 1)	7.0 (0 to 100)	7.6 (0 to 67)	4.6 (0 to 100)	
Trouble with Taste (Week 1 Day 1)	20.0 (0 to 100)	13.9 (0 to 100)	15.1 (0 to 100)	
Trouble with Taste (Week 7 Day 1)	18.5 (0 to 100)	15.2 (0 to 67)	12.9 (0 to 100)	
Flatulence (Week 1 Day 1)	18.3 (0 to 100)	19.5 (0 to 100)	23.1 (0 to 100)	
Flatulence (Week 7 Day 1)	12.4 (0 to 67)	16.1 (0 to 67)	12.4 (0 to 33)	
Faecal Incontinence (Week 1 Day 1)	8.9 (0 to 100)	8.8 (0 to 100)	7.1 (0 to 67)	
Faecal Incontinence (Week 7 Day 1)	2.5 (0 to 33)	7.3 (0 to 67)	3.1 (0 to 33)	
Sore Skin (Week 1 Day 1)	9.6 (0 to 67)	8.8 (0 to 67)	6.0 (0 to 33)	

Sore Skin (Week 7 Day 1)	11.6 (0 to 33)	9.7 (0 to 67)	4.2 (0 to 67)	
Embarrassed by Bowel Movement (Week 1 Day 1)	8.5 (0 to 100)	7.8 (0 to 100)	13.9 (0 to 100)	
Embarrassed by Bowel Movement (Week 7 Day 1)	7.5 (0 to 67)	8.1 (0 to 67)	10.4 (0 to 67)	
Stoma Care Problem (Week 1 Day 1)	16.6 (0 to 100)	3.3 (0 to 33)	6.6 (0 to 67)	
Stoma Care Problem (Week 7 Day 1)	9.9 (0 to 33)	2.4 (0 to 33)	8.3 (0 to 33)	
Impotence (Week 1 Day 1)	46.9 (0 to 100)	38.7 (0 to 100)	49.5 (0 to 100)	
Impotence (Week 7 Day 1)	40.4 (0 to 100)	42.7 (0 to 100)	50.7 (0 to 100)	
Dyspareunia (Week 1 Day 1)	12.1 (0 to 100)	7.2 (0 to 33)	11.0 (0 to 100)	
Dyspareunia (Week 7 Day 1)	14.3 (0 to 67)	10.3 (0 to 33)	13.3 (0 to 67)	

Notes:

[8] - Overall number of subjects analyzed was 83. Number of subjects analyzed varied per visit.

[9] - Overall number of subjects analyzed was 86. Number of subjects analyzed varied per visit.

[10] - Overall number of subjects analyzed was 85. Number of subjects analyzed varied per visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Assessed by FACT-EGFRI-18 for Skin Rash

End point title	Quality of Life Assessed by FACT-EGFRI-18 for Skin Rash
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End point description:

Scale: Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18).

The FACT-EGFRI-18 is an 18-question scale used to assess EGFR-inhibitor-treated cancer patients' quality of life relative to their experience of skin rash based on three (3) multi-item subscales. The subscales combined (i.e., Symptom Index) range in score from 0 to 72. A higher score represents a high level of symptomatology (problems).

High scores for all subscales represent a worse outcome:

- The Physical subscale ranges in score from 0 to 28.
- The Social/Emotional subscale ranges in score from 0 to 24.
- The Functional subscale ranges in score from 0 to 20.

This measure was self-reported. Numbers analyzed between Week 1 and Week 4 differ from each other, as well from the overall number of subjects analyzed. Data could not be collected from subjects not compliant with reporting or once discontinued.

End point type	Secondary
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End point timeframe:

Assessed every 3 weeks (week 1 and week 4 reported)

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83 ^[11]	86 ^[12]	85 ^[13]	
Units: score on a scale				
arithmetic mean (full range (min-max))				
Physical (Week 1 Day 1)	22.9 (2 to 28)	23.1 (4 to 28)	24.3 (6 to 28)	
Physical (Week 4 Day 1)	18.0 (4 to 28)	19.7 (5 to 28)	25.1 (16 to 28)	
Social/Emotional (Week 1 Day 1)	21.5 (9 to 24)	21.5 (6 to 24)	22.6 (9 to 24)	
Social/Emotional (Week 4 Day 1)	19.9 (7 to 24)	20.3 (5 to 24)	23.2 (15 to 24)	
Functional (Week 1 Day 1)	17.9 (5 to 20)	18.3 (7 to 20)	18.7 (4 to 20)	
Functional (Week 4 Day 1)	16.3 (3 to 20)	17.0 (6 to 20)	19.3 (13 to 20)	
Symptom Index (Week 1 Day 1)	62.3 (18 to 72)	62.9 (20 to 72)	65.6 (19 to 72)	

Symptom Index (Week 4 Day 1)	54.2 (16 to 72)	57.0 (22 to 72)	67.6 (46 to 72)	
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Notes:

[11] - Overall number of subjects analyzed was 83. Number of subjects analyzed varied per visit.

[12] - Overall number of subjects analyzed was 86. Number of subjects analyzed varied per visit.

[13] - Overall number of subjects analyzed was 85. Number of subjects analyzed varied per visit.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival (OS) Time for Patients in Europe + United States With Double-Negative mCRC (EU+US DNmCRC)

End point title	Overall Survival (OS) Time for Patients in Europe + United States With Double-Negative mCRC (EU+US DNmCRC)
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End point description:

This endpoint is exploratory. Because of the unanticipated long OS in the control group, initial exploratory subgroup analyses identified that findings in patients enrolled in Russia differed when compared with patients enrolled in the ITT subpopulation and the EU+US subpopulation. For this reason, subjects in Russia were excluded from further exploratory subset analyses that evaluated the effects of genomic parameters known to impact patient responses to anti-EGFR mAbs. Removal of the outlier Russian patients provided a patient population that was more homogeneous with respect to their prior treatment regimens, thereby facilitating further exploratory analyses. If a subject had not died, survival time was censored at the last date the subject was known to be alive.

The analysis population was the EU+US DNmCRC analysis set, which is a genomically-defined subpopulation excluding patients with high frequency clonal RAS mutations and BRAF V600E mutations.

End point type	Post-hoc
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End point timeframe:

From randomization until the date of death (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62 ^[14]	57 ^[15]	51 ^[16]	
Units: months				
median (confidence interval 95%)	8.9 (6.2 to 12.4)	11.9 (9.7 to 13.8)	8.4 (6.4 to 10.0)	

Notes:

[14] - Overall number of subjects analyzed for this endpoint.

[15] - Overall number of subjects analyzed for this endpoint.

[16] - Overall number of subjects analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival (OS) Time for Patients in Europe + United States With Triple-Negative mCRC (EU+US TNmCRC)

End point title	Overall Survival (OS) Time for Patients in Europe + United States With Triple-Negative mCRC (EU+US TNmCRC)
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End point description:

This outcome measure is exploratory. Because of the unanticipated long OS in the control group, initial exploratory subgroup analyses identified that findings in patients enrolled in Russia differed when

compared with patients enrolled in the ITT subpopulation and the EU+US subpopulation. For this reason, subjects in Russia were excluded from further exploratory subset analyses that evaluated the effects of genomic parameters known to impact patient responses to anti-EGFR mAbs. Removal of the outlier Russian patients provided a patient population that was more homogeneous with respect to their prior treatment regimens, thereby facilitating further exploratory analyses. If a subject had not died, survival time was censored at the last date the subject was known to be alive.

The analysis population was the EU+US TNmCRC analysis set, which is a genomically-defined subpopulation excluding DNmCRC patients with six (6) selected EGFR extracellular domain (ECD) mutations.

End point type	Post-hoc
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End point timeframe:

From randomization until the date of death (assessed up to 32 months).

End point values	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47 ^[17]	46 ^[18]	38 ^[19]	
Units: months				
median (confidence interval 95%)	10.6 (6.8 to 13.1)	12.8 (9.7 to 14.7)	7.3 (6.3 to 8.8)	

Notes:

[17] - Overall number of subjects analyzed for this endpoint.

[18] - Overall number of subjects analyzed for this endpoint.

[19] - Overall number of subjects analyzed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data were collected beginning with the signing of informed consent and continued through the End of Trial Intervention Visit (i.e., no earlier than 28 days after stop of treatment). The AE data collection period was 38 months.

Adverse event reporting additional description:

Subjects analyzed for serious AEs and non-serious AEs are based on the Safety Analysis Set. The Safety Analysis Set contained all subjects in the ITT Analysis Set who received at least one (1) dose of trial treatment (Sym004, 5-FU, or capecitabine) and in addition, those subjects who received Best Supportive Care only.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Arm A: Sym004 (12 mg/kg)
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Reporting group description:

Sym004 is a 1:1 mixture of two mAbs (futuximab and modotuximab) which bind to two non-overlapping epitopes of the EGFR.

Sym004 was administered as an intravenous infusion at a dose of 12 milligrams per kilogram (mg/kg) weekly until unacceptable toxicity, disease progression, or consent withdrawal.

Reporting group title	Arm B: Sym004 (9/6 mg/kg)
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Reporting group description:

Sym004 is a 1:1 mixture of two mAbs (futuximab and modotuximab) which bind to two non-overlapping epitopes of the EGFR.

Sym004 was administered as an intravenous infusion at a loading dose of 9 mg/kg followed by 6 mg/kg weekly until unacceptable toxicity, disease progression, or consent withdrawal.

Reporting group title	Arm C: Investigator's Choice
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Reporting group description:

Best supportive care (BSC) or Fluorouracil (5-FU, Adrucil) or Capecitabine (Xeloda) will be given as per Investigator's discretion. BSC was the best palliative care as per Investigator's discretion, excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions, and nutritional support. 5-FU was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert. Capecitabine was to be administered at doses and schedules as per Investigator's discretion and in line with the local package insert.

Serious adverse events	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 83 (32.53%)	23 / 84 (27.38%)	12 / 78 (15.38%)
number of deaths (all causes)	68	62	57
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			

subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 83 (2.41%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 83 (0.00%)	2 / 84 (2.38%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 83 (2.41%)	2 / 84 (2.38%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Cardiac failure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus node dysfunction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 83 (2.41%)	2 / 84 (2.38%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal varices haemorrhage			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal obstruction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 83 (2.41%)	0 / 84 (0.00%)	3 / 78 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin toxicity			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesicocutaneous fistula			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacteraemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 83 (1.20%)	2 / 84 (2.38%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 84 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	4 / 83 (4.82%)	5 / 84 (5.95%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	4 / 4	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: Sym004 (12 mg/kg)	Arm B: Sym004 (9/6 mg/kg)	Arm C: Investigator's Choice
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 83 (100.00%)	84 / 84 (100.00%)	67 / 78 (85.90%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 83 (7.23%)	2 / 84 (2.38%)	1 / 78 (1.28%)
occurrences (all)	7	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 83 (31.33%)	21 / 84 (25.00%)	14 / 78 (17.95%)
occurrences (all)	34	28	16
Chills			
subjects affected / exposed	3 / 83 (3.61%)	5 / 84 (5.95%)	1 / 78 (1.28%)
occurrences (all)	3	7	1
Fatigue			

subjects affected / exposed	8 / 83 (9.64%)	7 / 84 (8.33%)	14 / 78 (17.95%)
occurrences (all)	9	7	16
Mucosal inflammation			
subjects affected / exposed	8 / 83 (9.64%)	6 / 84 (7.14%)	4 / 78 (5.13%)
occurrences (all)	10	6	4
Oedema peripheral			
subjects affected / exposed	9 / 83 (10.84%)	7 / 84 (8.33%)	1 / 78 (1.28%)
occurrences (all)	9	7	1
Pyrexia			
subjects affected / exposed	12 / 83 (14.46%)	10 / 84 (11.90%)	9 / 78 (11.54%)
occurrences (all)	20	11	9
Xerosis			
subjects affected / exposed	26 / 83 (31.33%)	12 / 84 (14.29%)	0 / 78 (0.00%)
occurrences (all)	28	20	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 83 (3.61%)	5 / 84 (5.95%)	5 / 78 (6.41%)
occurrences (all)	3	7	5
Dyspnoea			
subjects affected / exposed	5 / 83 (6.02%)	3 / 84 (3.57%)	6 / 78 (7.69%)
occurrences (all)	5	3	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 83 (10.84%)	2 / 84 (2.38%)	0 / 78 (0.00%)
occurrences (all)	9	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 83 (8.43%)	8 / 84 (9.52%)	0 / 78 (0.00%)
occurrences (all)	10	11	0
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 83 (9.64%)	6 / 84 (7.14%)	1 / 78 (1.28%)
occurrences (all)	9	8	1
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 83 (8.43%)	10 / 84 (11.90%)	6 / 78 (7.69%)
occurrences (all)	8	12	9
Blood bilirubin increased			

subjects affected / exposed	5 / 83 (6.02%)	2 / 84 (2.38%)	1 / 78 (1.28%)
occurrences (all)	5	3	1
Electrocardiogram QT prolonged			
subjects affected / exposed	6 / 83 (7.23%)	7 / 84 (8.33%)	2 / 78 (2.56%)
occurrences (all)	12	11	2
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	18 / 83 (21.69%)	15 / 84 (17.86%)	0 / 78 (0.00%)
occurrences (all)	20	18	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 83 (8.43%)	11 / 84 (13.10%)	7 / 78 (8.97%)
occurrences (all)	12	17	10
Supraventricular extrasystoles			
subjects affected / exposed	1 / 83 (1.20%)	5 / 84 (5.95%)	2 / 78 (2.56%)
occurrences (all)	1	5	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 83 (12.05%)	15 / 84 (17.86%)	11 / 78 (14.10%)
occurrences (all)	12	21	17
Leukopenia			
subjects affected / exposed	4 / 83 (4.82%)	7 / 84 (8.33%)	5 / 78 (6.41%)
occurrences (all)	4	8	12
Neutropenia			
subjects affected / exposed	2 / 83 (2.41%)	4 / 84 (4.76%)	9 / 78 (11.54%)
occurrences (all)	2	9	13
Thrombocytopenia			
subjects affected / exposed	3 / 83 (3.61%)	7 / 84 (8.33%)	8 / 78 (10.26%)
occurrences (all)	3	13	14
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 83 (15.66%)	10 / 84 (11.90%)	3 / 78 (3.85%)
occurrences (all)	20	10	3
Abdominal pain upper			
subjects affected / exposed	2 / 83 (2.41%)	0 / 84 (0.00%)	4 / 78 (5.13%)
occurrences (all)	2	0	4

Constipation			
subjects affected / exposed	6 / 83 (7.23%)	3 / 84 (3.57%)	6 / 78 (7.69%)
occurrences (all)	6	3	6
Diarrhoea			
subjects affected / exposed	10 / 83 (12.05%)	19 / 84 (22.62%)	20 / 78 (25.64%)
occurrences (all)	17	25	27
Nausea			
subjects affected / exposed	9 / 83 (10.84%)	10 / 84 (11.90%)	12 / 78 (15.38%)
occurrences (all)	12	11	13
Stomatitis			
subjects affected / exposed	8 / 83 (9.64%)	4 / 84 (4.76%)	0 / 78 (0.00%)
occurrences (all)	9	5	0
Vomiting			
subjects affected / exposed	6 / 83 (7.23%)	4 / 84 (4.76%)	6 / 78 (7.69%)
occurrences (all)	7	4	7
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	68 / 83 (81.93%)	65 / 84 (77.38%)	1 / 78 (1.28%)
occurrences (all)	96	93	1
Dry skin			
subjects affected / exposed	8 / 83 (9.64%)	10 / 84 (11.90%)	1 / 78 (1.28%)
occurrences (all)	12	12	1
Erythema			
subjects affected / exposed	16 / 83 (19.28%)	11 / 84 (13.10%)	0 / 78 (0.00%)
occurrences (all)	25	13	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	14 / 78 (17.95%)
occurrences (all)	1	2	18
Photosensitivity reaction			
subjects affected / exposed	10 / 83 (12.05%)	4 / 84 (4.76%)	0 / 78 (0.00%)
occurrences (all)	16	5	0
Pruritus			
subjects affected / exposed	33 / 83 (39.76%)	30 / 84 (35.71%)	2 / 78 (2.56%)
occurrences (all)	45	38	2
Rash			

subjects affected / exposed occurrences (all)	7 / 83 (8.43%) 16	6 / 84 (7.14%) 17	0 / 78 (0.00%) 0
Skin fissures subjects affected / exposed occurrences (all)	14 / 83 (16.87%) 16	16 / 84 (19.05%) 22	2 / 78 (2.56%) 4
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5	5 / 84 (5.95%) 6	7 / 78 (8.97%) 7
Muscle spasms subjects affected / exposed occurrences (all)	3 / 83 (3.61%) 4	5 / 84 (5.95%) 5	1 / 78 (1.28%) 1
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	13 / 83 (15.66%) 21	8 / 84 (9.52%) 10	1 / 78 (1.28%) 1
Paronychia subjects affected / exposed occurrences (all)	15 / 83 (18.07%) 22	18 / 84 (21.43%) 20	3 / 78 (3.85%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	5 / 84 (5.95%) 6	0 / 78 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5	3 / 84 (3.57%) 3	1 / 78 (1.28%) 2
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	20 / 83 (24.10%) 23	9 / 84 (10.71%) 9	7 / 78 (8.97%) 9
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 83 (4.82%) 5	5 / 84 (5.95%) 8	2 / 78 (2.56%) 2
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	5 / 84 (5.95%) 6	0 / 78 (0.00%) 0
Hypoalbuminaemia			

subjects affected / exposed	3 / 83 (3.61%)	5 / 84 (5.95%)	1 / 78 (1.28%)
occurrences (all)	3	11	1
Hypocalcaemia			
subjects affected / exposed	9 / 83 (10.84%)	8 / 84 (9.52%)	2 / 78 (2.56%)
occurrences (all)	13	10	2
Hypokalaemia			
subjects affected / exposed	10 / 83 (12.05%)	4 / 84 (4.76%)	3 / 78 (3.85%)
occurrences (all)	14	4	3
Hypomagnesaemia			
subjects affected / exposed	57 / 83 (68.67%)	47 / 84 (55.95%)	6 / 78 (7.69%)
occurrences (all)	84	72	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	Amendment 1: Extended the planned end of trial date. Added pregnancy testing during screening and treatment periods. Revised the IDMC meeting frequency and responsibilities. Removed stratification by intended treatment (Best Supportive Care vs. active anticancer treatment) and required subjects to be randomized in the ratio of 1:1:1 to Sym004 Arms A and B and the control group. Removed biweekly dosage and the option for an 18 mg/kg dose per application (i.e., dose). Added subject monitoring for 1 hour post-infusion. Revised dose reduction rules/added dose reduction for Sym004-induced reactions (rash, xerosis, paronychia, pruritus, and photosensitivity). Removed tumor node metastases staging at trial entry.
13 March 2015	Amendment 2: Updated sponsor and medical monitor information.
27 January 2016	Amendment 3: Updated the definition of end of trial, extended the trial minimum survival follow-up, and updated the primary endpoint statistical analysis. Clarified the subject weight to be used for trial drug administration and the use of low potency steroid creams. Further detailed the process for receipt of trial treatment by the Investigator. Clarified when the End of Treatment Visit was performed.
25 October 2016	Amendment 4: Updated biomarkers to be evaluated and clarified the reduction of data collection after the primary analysis was performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Considering the hypothesis-generating nature of a phase 2 clinical trial, the intent-to-treat (ITT) analysis should be viewed as the starting point of a scientific investigation process, not the final conclusion.

Notes: