



Clinical trial results:

An Open-label, Multi-Center Phase 1b/2a Trial Investigating Different Doses of Sym004 in Combination with FOLFIRI in Patients with Metastatic Colorectal Cancer Progressing after First-Line Therapy Summary

EudraCT number	2015-003047-19
Trial protocol	ES
Global end of trial date	05 May 2018

Results information

Result version number	v1 (current)
This version publication date	30 March 2019
First version publication date	30 March 2019

Trial information

Trial identification

Sponsor protocol code	Sym004-09
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02568046
WHO universal trial number (UTN)	-

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	15 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2017
Global end of trial reached?	Yes
Global end of trial date	05 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objective of Dose-Escalation Phase (Phase 1b):

To determine the MTD and RP2D of Sym004 when administered by intravenous (IV) infusion every second week in combination with a standard dosing regimen of FOLFIRI to patients with locally advanced or metastatic colorectal cancer (CRC).

Primary Objective of Dose-Expansion Phase (Phase 2a):

To evaluate the antineoplastic effect of Sym004 when administered at the RP2D in combination with FOLFIRI to patients with locally advanced or metastatic CRC.

In January 2017, the trial was terminated during Phase 1b and enrollment was prematurely discontinued. The primary objective changed to assess the safety of the treatment combination; collection of data for secondary and exploratory objectives was omitted.

Protection of trial subjects:

The potential to slow infusions, interrupt dosing, decrease the doses administered, and to discontinue administration of Sym004 in the event of specific AEs was outlined. In addition, steps to prevent infusion reactions and measures to intervene in the event of electrolyte imbalances and cutaneous toxicities were specified. Furthermore, prophylactic treatment for FOLFIRI-induced diarrhea and vomiting according to institutional standards was required.

Sym004 infusions were administered under the close supervision of an experienced physician in an environment where full resuscitation facilities were immediately available. At the end of each infusion, the IV line remained in place for at least 1 hour to allow administration of IV drugs, if necessary. Patients were carefully observed for a minimum of 2 hours following completion of the first administration of Sym004 and a minimum of 1 hour following completion of subsequent administrations.

Background therapy:

All patients received a standard dosing regimen of FOLFIRI. The standard regimen consists of Irinotecan (180 mg/m² IV, infused over 60-90 minutes) concurrently with Folinic Acid (400 mg/m² IV, infused over 120 minutes) followed by 5-FU (400 mg/m² IV bolus, then 2400 mg/m² infused over 46 hours).

Evidence for comparator: -

Actual start date of recruitment	15 March 2016
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	Spain: 5
Country: Number of subjects enrolled	United States: 5

Worldwide total number of subjects	10
EEA total number of subjects	5

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)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in March 2016. In January 2017, the trial was terminated early and enrollment was prematurely discontinued.

Pre-assignment

Screening details:

Male or female, 18 years of age at the time of informed consent. ECOG PS of 0 or 1. Histologically or cytologically confirmed, locally advanced or metastatic CRC documented to be without KRAS or NRAS gene mutations. Failed treatment for locally advanced or metastatic disease. Eligible for FOLFIRI. Measurable disease according to RECIST v1.1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sym004, 12 mg/kg + FOLFIRI

Arm description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

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 diluted in saline in an infusion bag prior to administration. The infusion had to be completed within 12 hours of preparation of the infusion bag.

All patients were given IV infusions of Sym004, administered every second week (Day 1 and Day 15 of each 28 day cycle \pm 2 days) through a peripheral line or indwelling catheter, and with the use of an infusion pump and an inline filter. Sym004 was dosed according to body weight. The allocated dose level was confirmed in writing by Sponsor or designee on an allocation form.

Arm title	Sym004, 9 mg/kg + FOLFIRI
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Arm description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Arm type	Experimental
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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 diluted in saline in an infusion bag prior to administration. The infusion had to be completed within 12 hours of preparation of the infusion bag.

All patients were given IV infusions of Sym004, administered every second week (Day 1 and Day 15 of each 28 day cycle \pm 2 days) through a peripheral line or indwelling catheter, and with the use of an infusion pump and an inline filter. Sym004 was dosed according to body weight. The allocated dose level was confirmed in writing by Sponsor or designee on an allocation form.

Number of subjects in period 1	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI
Started	5	5
Completed	5	5

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sym004, 12 mg/kg + FOLFIRI

Arm description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

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 diluted in saline in an infusion bag prior to administration. The infusion had to be completed within 12 hours of preparation of the infusion bag.

All patients were given IV infusions of Sym004, administered every second week (Day 1 and Day 15 of each 28 day cycle \pm 2 days) through a peripheral line or indwelling catheter, and with the use of an

infusion pump and an inline filter. Sym004 was dosed according to body weight. The allocated dose level was confirmed in writing by Sponsor or designee on an allocation form.

Arm title	Sym004, 9 mg/kg + FOLFIRI
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Arm description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

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 diluted in saline in an infusion bag prior to administration. The infusion had to be completed within 12 hours of preparation of the infusion bag.

All patients were given IV infusions of Sym004, administered every second week (Day 1 and Day 15 of each 28 day cycle \pm 2 days) through a peripheral line or indwelling catheter, and with the use of an infusion pump and an inline filter. Sym004 was dosed according to body weight. The allocated dose level was confirmed in writing by Sponsor or designee on an allocation form.

Number of subjects in period 2	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI
Started	5	5
Completed	0	2
Not completed	5	3
Consent withdrawn by subject	2	1
Other event	-	1
Adverse event, non-fatal	-	1
Death	2	-
Progressive disease	1	-

Baseline characteristics

Reporting groups

Reporting group title	Sym004, 12 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group title	Sym004, 9 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group values	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI	Total
Number of subjects	5	5	10
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)	1	4	5
From 65-84 years	4	1	5
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	69.3	61.1	
standard deviation	± 8.55	± 9.95	-
Gender categorical			
Units: Subjects			
Female	2	2	4
Male	3	3	6
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	4	3	7
Unknown or Not Responded	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	5	10
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment			
Units: Subjects			
United States	3	2	5
Spain	2	3	5
Height			
Units: centimeters (cm)			
arithmetic mean	170.4	171.3	
standard deviation	± 8.57	± 4.47	-
Weight			
Units: kilograms (kg)			
arithmetic mean	76.6	82.5	
standard deviation	± 11.97	± 16.10	-
Body Mass Index (BMI)			
Units: kg/m ²			
arithmetic mean	26.5	28.0	
standard deviation	± 4.20	± 4.52	-
Body Surface Area			
Units: m ²			
arithmetic mean	1.9	2.0	
standard deviation	± 0.17	± 0.24	-

End points

End points reporting groups

Reporting group title	Sym004, 12 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group title	Sym004, 9 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group title	Sym004, 12 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group title	Sym004, 9 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 non-overlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Primary: Number of Participants With Adverse Events (AEs) by Nature, Severity, and Occurrence Measured From Baseline to End of Trial Participation, as Assessed by the Common Terminology Criteria for AEs (Version 4.03) (CTCAE v4.03).

End point title	Number of Participants With Adverse Events (AEs) by Nature, Severity, and Occurrence Measured From Baseline to End of Trial Participation, as Assessed by the Common Terminology Criteria for AEs (Version 4.03) (CTCAE v4.03). ^[1]
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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 (e.g., treatment-emergent AE [TEAE]) were summarized according to MedDRA system organ classes and preferred terms. An AE was considered as treatment-emergent if it occurred after the first treatment administration. All safety analyses were conducted using the Full Analysis Set (FAS) population, defined as all patients who received at least 1 dose of trial treatment.

End point type	Primary
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End point timeframe:

15 Months

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: Because the trial was discontinued prematurely for business reasons, no formal efficacy analyses were conducted.

End point values	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Participants				
At least 1 TEAE	5	5		
At least 1 Serious TEAE	3	2		
At least 1 Serious TEAE related to Sym004 only	0	0		
At least 1 TEAE leading to Sym004 dose reduction	1	2		
At least 1 TEAE leading to interruption of Sym004	3	5		
At least 1 TEAE leading to Sym004 withdrawal	2	2		
At least 1 TEAE leading to FOLFIRI withdrawal	1	2		
At least 1 TEAE leading to trial termination	0	1		
At least 1 TEAE related to Sym004 + FOLFIRI	4	3		
At least 1 TEAE related to Sym004 only	4	5		
At least 1 TEAE related to FOLFIRI only	4	4		
At least 1 TEAE Grade ≥ 3 related to Sym004+FOLFIRI	2	2		
At least 1 TEAE Grade ≥ 3 related to Sym004 only	0	2		
At least 1 TEAE Grade ≥ 3 related to FOLFIRI only	1	1		
At least 1 dermatologic toxicity	3	5		
At least 1 TEAE of hypomagnesaemia	3	0		
At least 1 infusion related reaction TEAE	3	3		
At least 1 TEAE resulting in death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event data collection period was 15 months.

Adverse event reporting additional description:

AEs were collected from the signing of informed consent and continued 1 month (i.e., at least 28 days) after the last administration of treatment (i.e., after both Sym004 and FOLFIRI were discontinued). After the decision was made to prematurely discontinue the trial, collection of AEs continued 1 month after the last administration of Sym004.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Sym004, 12 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level 1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 nonoverlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Reporting group title	Sym004, 9 mg/kg + FOLFIRI
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Reporting group description:

Phase 1b, Dose-Escalation: Dose Level -1

IMP: Sym004, a 1:1 mixture of 2 monoclonal antibodies (mAbs) which bind specifically to 2 nonoverlapping epitopes of the epidermal growth factor receptor (EGFR).

Background Therapy: FOLFIRI (standard regimen)

Serious adverse events	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Sym004, 12 mg/kg + FOLFIRI	Sym004, 9 mg/kg + FOLFIRI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	3	
Chest discomfort			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	

Fatigue subjects affected / exposed occurrences (all)	4 / 5 (80.00%) 4	2 / 5 (40.00%) 2	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 5 (40.00%) 2	
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 5 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 5 (40.00%) 2	
Epistaxis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 5 (40.00%) 2	
Nasal inflammation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	0 / 5 (0.00%) 0	
Lipase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 5 (20.00%) 1	
Weight increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Injury, poisoning and procedural			

complications			
Infusion related reaction			
subjects affected / exposed	3 / 5 (60.00%)	3 / 5 (60.00%)	
occurrences (all)	4	3	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Aphasia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	4 / 5 (80.00%)	
occurrences (all)	1	6	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Chapped lips			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	
occurrences (all)	6	3	
Dry mouth			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Odynophagia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	
occurrences (all)	4	3	
Vomiting			

subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	3 / 5 (60.00%) 3	
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatitis acneiform subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	5 / 5 (100.00%) 5	
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Dry skin subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 5 (40.00%) 2	
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Skin fissures subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 5 (20.00%) 1	
Skin toxicity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Cystitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Hordeolum			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Influenza subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Paronychia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Pneumonia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3	0 / 5 (0.00%) 0	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	
Hypomagnesaemia subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 5	0 / 5 (0.00%) 0	
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	
Hypovolaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2015	1. Increased the blood volume collected for the biomarker samples. A larger volume of blood, and subsequent plasma, was needed for biomarker analysis when using Next-Generation Sequencing (NGS). 2. Timing for collection of AEs and SAEs was extended to allow total safety surveillance to include analysis of unanticipated problems having to do with overall trial conduct. This would include any adverse effects that may occur from protocol-specific investigations at screening.
05 August 2016	1. Added additional dose levels to facilitate further exploration of the safety and tolerability of Sym004. 2. Initiated mandatory prophylaxis for diarrhea in Cycle 1 with potential to continue in later cohorts. 3. Modified the inclusion and exclusion criteria section to allow enrollment of patients who progressed > 3 months after last dose and to allow enrollment of patients treated with drugs that potentially could cause QT prolongation. 4. Removed Sym004 dose-adjustment for obese patients. 5. Clarification of biomarker testing from collected tumor biopsies and revision of the tumor marker section to only collect CEA. 6. Modified the statistical section to clarify the number of patients required and added relevant references. 7. Specified grading of adverse events when there are changes in severity.
22 February 2017	1. Explanation included for prematurely discontinuing trial enrollment. 2. Changed the visit schedule for treatment and follow-up to apply only until Sym004 has been discontinued. 3. Omitted collection of non-safety related assessments and modified the statistical section to further reduce the collection of data to information needed for safety reporting required by authorities. 4. Revised the AE/SAE reporting requirements for progression of disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 January 2017	The trial was terminated prematurely as development of Sym004 in combination with FOLFIRI was discontinued.	-

Notes:

Limitations and caveats

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

The trial was terminated as development of Sym004 in combination with FOLFIRI was discontinued. The primary objective changed to assess the safety of the treatment combination; collection of data for secondary and exploratory objectives was omitted.

Notes: