



CLINICAL TRIAL PROTOCOL

Trial Title:	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
Short Title:	Sym004 in Combination with FOLFIRI in Metastatic Colorectal Cancer Patients
Sponsor:	<u>Symphogen A/S</u> [REDACTED] [REDACTED] [REDACTED]
Sponsor's Medical Expert:	[REDACTED] [REDACTED]
Coordinating Investigator:	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
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Trial Phase:	Phase 1b/2a
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List of Responsible Person/ Contact Listing	Lists of Investigators responsible for conducting the trial, medically qualified physicians responsible for all trial site related medical decisions (if other than the Investigators), Monitors, clinical laboratories and other medical and/or

technical departments and/or institutions involved in the trial are provided as separate documents.

GCP Statement: The trial will be conducted in compliance with this Clinical Trial Protocol, ICH E6 GCP (1) and applicable regulations.

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Signature Page

Sponsor

I hereby approve the Clinical Trial Protocol as suitable and appropriate for use.

[Redacted]
[Redacted]
[Redacted]

Symphogen A/S

Signature Page

Principal Investigator

I, the undersigned, am responsible for the conduct of the trial at this site and agree;

- To assume responsibility for the proper conduct of the clinical trial at this Investigational Site
- Not to implement any changes to the Clinical Trial Protocol without agreement from the Sponsor and prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the patient
- That I am aware of, and will comply with “Good Clinical Practice” (ICH GCP) (CPMP/ICH/135/95) and all applicable regulatory requirements
- That all site staff to which I have delegated tasks for this clinical trial, are adequately informed about the investigational product(s) and of their trial-related duties and functions as described in the Clinical Trial Protocol

Signature

Date of Signature

Name:

Academic degree:

Function:

Institution:

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA19-9	Carbohydrate Antigen 19-9
CDC	Complement-Dependent Cytotoxicity
CEA	Carcinoembryonic Antigen
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLT	Dose-Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
CRF	Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
EOT	End of Treatment
FAS	Full Analysis Set
FFPE	Formalin Fixed Paraffin Embedded
FUP	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
HA	Health Authority
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors

ISMC	Independent Safety Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISF	Investigator Site File
iv	Intravenous
KRAS	Kirsten Rat Sarcoma
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
mAb992	Monoclonal Antibody 992 (futuximab)
mAb1024	Monoclonal Antibody 1024 (modotuximab)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image/Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NRAS	Neuroblastoma Rat Sarcoma
NSCLC	Non-Small Cell Lung Carcinoma
OR	Objective Response
PD	Progressive Disease
PK	Pharmacokinetic(s)
PO	Per Os
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QID	Four Times Per Day
RAS	Rat Sarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SOC	System Organ Class
SOI	Start of Infusion

SOP	Standard Operating Procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reactions
TdP	Torsade de Pointes
TEAE	Treatment Emergent Adverse Events
TID	Three Times Per Day
TNM	Tumor, Node, Metastasis
ULN	Upper Limit of Normal
WT	Wild Type

PHARMACOKINETIC TERMS

AUC	Area under the concentration-time curve
AUC _{Norm 0-336h}	Dose-normalized area under the concentration-time curve from end of infusion to 336 hours
CL	Clearance
C _{max}	Maximum concentration
C _{trough}	Trough Concentration
T _{1/2}	Elimination half-life
T _{max}	Time of maximum concentration
V	Volume of distribution

OTHER TERMS

Baseline	The value measured at Day 1 of Cycle 1, before initiation of Sym004. For variables/assessments not scheduled to be performed at that time point or that are missing at baseline, the baseline value is the value from the screening period measured closest to Day 1 of Cycle 1
FA	Folinic Acid
5-FU	Fluorouracil
FOLFIRI	Combination of FOL inic Acid (FA), F luorouracil (5-FU) and IRI notecan (irinotecan)
FOLFOX	Combination of FOL inic Acid (FA), F luorouracil (5-FU) and OX aliplatin (oxaliplatin)

2 SYNOPSIS

Trial Title	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
Trial ID and Phase	Sym004-09, Phase 1b/2a
Trial Sites and Countries	Dose-escalation: Approximately 8 investigational trial sites Dose-expansion: 10 to 15 investigational trial sites Expected countries: USA and countries within the EU
Planned Trial Period	The dose-escalation phase of the trial is expected to begin Q4 2015. Patients will be sequentially enrolled to dose-escalation cohorts until establishment of the Maximum Tolerated Dose (MTD) and/or Recommended Phase 2 Dose (RP2D), expectedly Q4 2016. The dose-expansion phase of the trial is expected to begin Q4 2016 with enrollment to be completed Q2-Q3 2017.
Objectives	<p>Primary Objective of Dose-Escalation Phase (Phase 1b): To determine the MTD and/or RP2D of Sym004 when administered by intravenous (iv) infusion every second week in combination with a standard dosing regimen of FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) to patients with locally advanced or metastatic colorectal cancer (CRC).</p> <p>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.</p> <p>As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, the primary, secondary, and exploratory objectives are no longer applicable. Clinical safety-related evaluations will continue to be conducted.</p>
Endpoints	<p><u>The Primary Endpoint of the Dose-Escalation Phase</u> is the occurrence of Dose-Limiting Toxicities (DLT) observed during Cycle 1 of Sym004 administration in combination with FOLFIRI.</p> <p><u>The Primary Endpoint of the Dose-Expansion Phase</u> is confirmed objective antitumor response.</p> <p>As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, only the clinical safety-related evaluations will continue to be conducted.</p>
Design and Plan	<p><u>Screening Period:</u> After providing informed consent, the eligibility of patients will be established according to the protocol-defined inclusion and exclusion criteria. Once all screening procedures have been completed and eligibility has been confirmed, a blood and urine sample will be taken for biomarker analysis. Furthermore, if an archived tumor tissue biopsy sample for central evaluation of RAS mutations is not available, the patient will have a tumor biopsy performed.</p> <p>Eligible patients will be enrolled into the trial and enter the treatment period.</p> <p><u>Treatment Period:</u> During the dose-escalation phase, patients will be assigned consecutively to the next available open treatment cohort and will receive Sym004 in combination with FOLFIRI. Dose escalation will continue in patient cohorts until determination of the MTD. If the MTD is not formally reached, the Independent</p>

	<p>Safety Monitoring Committee (ISMC) will together with the Sponsor declare the RP2D based on the available safety data.</p> <p>Once the RP2D has been identified, all subsequent patients will be enrolled into the dose-expansion cohort and will receive the RP2D dose of Sym004 in combination with FOLFIRI.</p> <p>Sym004 and FOLFIRI are both initiated on Day 1 of Cycle 1 (in the following C1/D1).</p> <p>Patients in the trial will receive iv infusions every second week of Sym004 in combination with a defined FOLFIRI regimen until occurrence of any of the following: Unacceptable toxicity or other conditions preventing further administration, Progressive Disease (PD), termination of the trial, or patient’s decision to withdraw. Patients may discontinue treatment (Sym004 and FOLFIRI) simultaneously; may discontinue Sym004 before discontinuing FOLFIRI; or may discontinue FOLFIRI before discontinuing Sym004.</p> <p>The visit schedule for the treatment period will apply until both Sym004 and FOLFIRI have been discontinued.</p> <p><u>End of Treatment/Follow-up:</u> Once both Sym004 and FOLFIRI have been discontinued, an End of Treatment Visit (EOT) will be performed within 10 days from the decision to withdraw treatment.</p> <p>A follow-up visit will be performed 1 month after the last administration of Sym004/FOLFIRI (i.e. only after both treatments have been discontinued). This One Month Follow-up (1M FUP) visit, will constitute the end of trial participation for the patient.</p> <p>As of Amendment 3: This amendment to the clinical trial protocol (CTP) is based on a Sponsor decision to discontinue the development of Sym004 in combination with FOLFIRI. As a result, enrollment has stopped and a reduction in the total scope of non-safety related assessments being conducted under this CTP will be implemented.</p> <p>Patients who are actively being treated with Sym004 alone or in combination with FOLFIRI may continue therapy until unacceptable toxicity or other conditions preventing further administration, progressive disease (PD), or patient’s decision to withdraw. <u>Patients no longer receiving Sym004 alone or in combination with FOLFIRI should be discontinued from study participation.</u></p> <p>Patients will continue to be followed and assessed for clinical safety-related concerns throughout their respective treatment periods and at minimum for 30 days after the last administration of Sym004.</p>
<p>Number of Patients</p>	<p>In total, 50 patients are planned to be treated with Sym004 in combination with FOLFIRI.</p> <p>The number of patients treated during the dose-escalation phase will depend upon the observed tolerability of Sym004 in combination with FOLFIRI. Up to approximately 18 patients are expected to be treated during the dose-escalation</p>

	<p>phase. Enrollment in the dose-expansion phase will continue until a total of 50 patients have been enrolled in dose-escalation and dose-expansion phases combined.</p>
<p>Diagnosis and Main Inclusion and Exclusion Criteria</p>	<p>Patients with locally advanced or metastatic CRC, wild type KRAS/NRAS (exon 2, 3, 4) will be enrolled.</p> <p><u>Main Inclusion Criteria include:</u></p> <ul style="list-style-type: none"> • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Failed* prior adjuvant therapy or prior therapy for treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab. *Failure is defined as radiologic progression • Eligible for FOLFIRI • Measurable disease according to RECIST v1.1 <p><u>Main Exclusion Criteria include:</u></p> <ul style="list-style-type: none"> • Prior therapy with anti-EGFR antibodies, anti-EGFR small molecule inhibitors or irinotecan (CPT-11) • Discontinuation of prior therapy with oxaliplatin and a fluoropyrimidine due to diarrhea \geq Grade 3 • Any antineoplastic agent (standard or investigational) within 4 weeks prior to first administration of trial treatments • Significant gastrointestinal abnormalities, as per defined criteria • Significant cardiovascular disease, as per defined criteria • Abnormal hematologic, renal or hepatic function, as per defined criteria
<p>Investigational Medicinal Product, Dose(s) and Treatment Schedule</p>	<p>The Investigational Medicinal Product (IMP) is Sym004. Sym004 is a 1:1 mixture of 2 monoclonal Antibodies (mAbs), which bind specifically to 2 non-overlapping epitopes of the Epidermal Growth Factor Receptor (EGFR).</p> <p>In this trial, Sym004 is administered in combination with a standard dosing regimen of FOLFIRI. Both therapies/regimens will be administered every second week by iv infusion (Day 1 and Day 15 of each 28 day cycle, \pm 2 days).</p> <p><u>Dose-Escalation</u> During the dose-escalation phase of the trial, the following 3 dose levels of Sym004 will potentially be evaluated in combination with FOLFIRI:</p> <ul style="list-style-type: none"> • Dose Level 1: Sym004 12 mg/kg + FOLFIRI • Dose Level 2: Sym004 15 mg/kg + FOLFIRI • Dose Level 3: Sym004 18 mg/kg + FOLFIRI <p>If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, successive lower dose levels will be explored:</p> <ul style="list-style-type: none"> • Dose Level -1: Sym004 9 mg/kg + FOLFIRI • Dose Level -2: Sym004 9 mg/kg (loading dose) + FOLFIRI followed by 6 mg/kg + FOLFIRI • Dose Level -3: Sym004 6 mg/kg + FOLFIRI <p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) has not exceeded the MTD and is well tolerated during Cycle 1, but overall tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose Level -2 may be explored.</p>

	<p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) during Cycle 1 has not exceeded the MTD, but tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose-Level -3 may be explored.</p> <p>If the toxicity profile of lower doses where mandatory diarrhea prophylaxis is utilized indicates that the dose is well tolerated, further evaluation of Dose Level 1, and potentially Dose Levels 2 and 3 may take place after approval by the ISMC.</p> <p>Dose-Expansion Once the RP2D has been determined during the dose-escalation phase, the enrollment into the dose-expansion phase will commence. All patients enrolled to this phase will be treated at the established RP2D of Sym004 in combination with FOLFIRI.</p>
<p>Criteria for Evaluation</p>	<p>All assessments are repeated throughout the trial at protocol specified intervals, unless otherwise stated.</p> <p>Safety Assessments</p> <ul style="list-style-type: none"> • Medication survey • (Serious) Adverse Event ([S]AE) survey • DLT evaluation (dose escalation only) during Cycle 1 with a final assessment 14 (±2) days after the last dose of Cycle 1 or on the scheduled first day of Cycle 2, prior to dosing • Vital signs and body weight • Eastern Cooperative Oncology Group (ECOG) performance status • Physical Examination • Dermatological Examination • Electrocardiogram (ECG) • Safety blood samples • Urinalysis • Pregnancy test <p>Disease Assessments</p> <ul style="list-style-type: none"> • (Archival) tumor tissue sample is requested at Screening after confirmation of eligibility • Tumor marker evaluation • Disease status evaluation by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) <p>Additional Assessments*</p> <ul style="list-style-type: none"> • Pharmacokinetic (PK) Sampling* • Anti-Drug Antibody (ADA) Testing* • Biomarker blood and urine sample* <p>*Omitted with Amendment 3</p>
<p>Statistical Methods and Sample Size Calculation</p>	<p>The primary endpoint of the <u>dose-escalation phase</u> is the occurrence of DLTs observed during Cycle 1 on each of the Sym004 dose levels given in combination with FOLFIRI. The number of enrolled patients will depend on the observed DLTs independently in each cohort. Based on a 3 + 3 design, it is planned to enroll between 9 and 18 patients during dose-escalation.</p>

	<p>In the <u>dose-expansion phase</u> of the trial, the primary endpoint is confirmed objective antitumor response to the combination of Sym004 and FOLFIRI. The number of patients planned to be included in this part of the trial is 32-41 patients depending on the number of patients enrolled in the dose-escalation phase.</p> <p>The planned number of patients to be enrolled is not based on a formal sample size calculation.</p>
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3 BACKGROUND AND RATIONALE

3.1 Disease and Treatment

3.1.1 Metastatic Colorectal Cancer

In 2012, the worldwide incidence of Colorectal Cancer (CRC) was estimated to be over 1.36 million (2). Curative surgical treatment is only possible in the early stages of the disease (Stage I/II) and if the malignancy has not spread beyond the regional lymph nodes (Stage III). Five-year survival for patients with Stage I CRC is approximately 90%. Survival decreases with increasing stage of disease, and the five-year survival of patients with Stage IV CRC, the patient population targeted in this trial, diminishes to approximately 12% (3).

3.1.2 Current Treatment of Metastatic Colorectal Cancer Disease

Metastatic CRC (mCRC) is treated with a variety of regimens of combination chemotherapy and targeted agents, including monoclonal Antibodies (mAbs) targeting the Epidermal Growth Factor Receptor (EGFR) (3-8). The approved anti-EGFR antibodies, cetuximab and panitumumab, have been shown to be active in first-, second-, and third-line therapy of CRC (3-8). Cetuximab and panitumumab have been shown to have single agent activity (7,8), and to increase the effectiveness of regimens including 5-Fluorouracil (5-FU), folinic acid, and irinotecan (e.g., FOLFIRI) in the first- and second-line treatment of CRC (3-8). Despite the clearly documented activity of anti-EGFR antibodies, many patients are refractory to these agents prior to beginning therapy, and patients who initially respond ultimately progress while on therapy. These findings led to exploration as to why patients responded so differently. Further analysis of these and other trials, documented that efficacy was only demonstrable in patients whose CRC expressed the Wild Type (WT) Kirsten Rat Sarcoma (KRAS) genotype, whereas patients with evidence of specific mutations in KRAS, exon 2, 3 and 4, and Neuroblastoma Rat Sarcoma (NRAS), exon 2, 3 and 4, in their tumors do not respond to treatment with anti-EGFR antibodies (7,8). Administration of anti-EGFR mAbs appears to have a deleterious effect in the latter population (7,8). Other factors have also been implicated in innate and acquired resistance to treatment with anti-EGFR antibodies.

3.2 Investigational Medicinal Product

3.2.1 Sym004

The Investigational Medicinal Product (IMP) tested in this trial is Sym004.

Sym004 is a 1:1 mixture of 2 recombinant, human-mouse chimeric, immunoglobulin G1 (IgG1) antibodies (referred to as mAb992 [futuximab] and mAb1024 [modotuximab]), which bind specifically to 2 non-overlapping epitopes of the EGFR.

Sym004 is a clear, colorless liquid to be administered as an intravenous (iv) infusion through a peripheral line or indwelling catheter.

3.2.2 Mechanism of Action

Sym004 binds to non-overlapping epitopes on domain III of the EGFR (9,10). The binding of Sym004 induces a distinct mechanism of action that is dependent on the presence of both antibodies. Sym004 induces highly efficient internalization of EGFR on cancer cells, and degradation of the internalized receptor protein that leads to down-regulation of EGFR and subsequent inhibition of cancer cell growth (9). There is considerable *in vitro* and *in vivo* evidence suggesting that Sym004 is superior to existing, marketed anti-EGFR antibodies (cetuximab and panitumumab) in a wide range of cancer models (9-11). Furthermore, Sym004 has demonstrable activity in cancer cells with acquired resistance to cetuximab (11).

3.2.3 Summary of Non-clinical Findings

A series of *in vitro* and *in vivo* studies were performed with Sym004 to support clinical trials in humans (9-12). The ability of Sym004 to inhibit the proliferation and motility of cancer cells was investigated *in vitro* in a range of human cancer cell lines, and compared to cetuximab as a reference anti-EGFR antibody (9,10). The effect of Sym004 on cells with acquired resistance to cetuximab was also investigated in several human cancer cell lines (11). Mechanistic studies of Sym004 action were performed using a panel of human cancer cell lines; testing included: Assessment of inhibition of ligand binding, EGFR activation, downstream signaling, EGFR internalization, and EGFR degradation (9). Sym004-mediated secondary effector functions, such as Antibody-Dependent Cellular Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC), were investigated using 51chromium-release assays and human cancer cell lines. The studies showed that Sym004 is superior at inhibiting EGFR activity compared to cetuximab and/or panitumumab, used as reference antibodies, *in vitro* through a mechanism of action (i.e., downregulation and degradation of the EGFR) that is dependent on the binding of both antibodies (9,11).

The activity of Sym004 was also investigated *in vivo* in several xenograft tumor models in mice, and was compared to cetuximab and/or panitumumab in these studies. In all models, Sym004 was either superior to or as efficient as these reference antibodies (9-11).

Toxicology studies in cynomolgus monkeys showed a toxicity profile consistent with other anti-EGFR antibodies, including documentation of dermatological and gastrointestinal toxicities (12).

3.2.4 Summary of Clinical Findings

Several clinical trials have been completed with Sym004, and other trials are ongoing or being initiated.

3.2.4.1 Safety

As of 30 Sep 2014, more than 175 patients with solid tumors, including but not limited to patients with recurrent/metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN), mCRC, and Non-Small Cell Lung Carcinoma (NSCLC), have been exposed to Sym004 in weekly doses of up to 12 mg/kg, and in every second week doses of up to 18

mg/kg. Analyses of Adverse Events (AEs) from the initial 2 clinical trials Sym004-01, a Phase 1 dose-escalation trial evaluating safety, tolerability, Pharmacokinetic (PK) and pharmacodynamic effects of Sym004, and Sym004-02, a phase 2 evaluation of patients with SCCHN who were refractory to anti-EGFR antibody therapy, have been performed. For EMR trial 200637-001, a trial of 2 regimens of Sym004 vs. chemotherapy in patients with CRC refractory to prior therapy with anti-EGFR mAbs, AE data are available for dose levels of 6 mg/kg (3 patients), as well as 9 + 6 mg/kg and 12 mg/kg weekly (6 patients each). For other ongoing clinical trials (Sym004-01 (Part F), EMR 200637-002, and EMR 200637-003), only data on Serious Adverse Events (SAEs) are available.

Skin toxicities, hypomagnesemia, and Infusion-Related Reactions (IRRs) are frequently observed after administration of anti-EGFR antibodies, and these toxicities were observed in patients receiving Sym004. Detailed data on these and other AEs are presented in the Investigator's Brochure (IB).

Anti-EGFR-related skin toxicities (including rash, pruritus, skin fissures, dry skin, erythema, and paronychia) have been observed in more than 90% of patients in the completed and ongoing clinical trials of Sym004. In patients who had previously received anti-EGFR mAb therapy, Grade 3 skin toxicities were reported frequently; and were noted in 33.3% and 41.2% of patients at dose levels of 12 mg/kg or 18 mg/kg, respectively, when Sym004 was administered every 2 weeks.

Mucositis was observed in up to 40% of patients, but only 1 patient experienced Grade 3 severity. Diarrhea has been reported in up to 59% of patients, with $\leq 10\%$ of patients having experienced Grade 3 diarrhea. Diarrhea was reported in 53.8% and 34.5% of patients receiving doses of 9 and 12 mg/kg weekly, respectively, and in 33.3% and 58.8% of patients at an every second week dose of 12 or 18 mg/kg, respectively. Nausea was reported in 33.3% and 11.8% of patients on an every second week dose of 12 or 18 mg/kg. Vomiting was reported in 25.0% and 5.9% of patients at an every second week dose of 12 or 18 mg/kg, respectively.

Electrolyte disturbances (in particular hypomagnesemia) often associated with anti-EGFR mAbs, were also frequently observed in the completed and ongoing trials of Sym004. In clinical trials for which all AE data are available, hypomagnesemia was reported in from 53.8 to 76.5% of patients. Hypomagnesemia was observed in 66.7% (\geq Grade 3; 25.0%) and 76.5% (\geq Grade 3; 35.3%) of patients receiving doses of 12 and 18 mg/kg every 2 weeks, respectively. Hypocalcemia was observed in 37.9% of patients receiving Sym004 at a dose of 12 mg/kg weekly, with 3 (10.3%) patients experiencing hypocalcemia \geq Grade 3. At the other dose levels, hypocalcemia occurred in $< 10\%$ of those treated, and Grade 3 events were not observed. In the Sym004-01 and the Sym004-02 clinical trials, hypomagnesemia represented the majority of SAEs that were considered to be related to Sym004 therapy. Serious clinical complications of hypomagnesemia have not been observed.

IRRs have also been observed. In all ongoing clinical trials, premedication with glucocorticosteroids and antihistamines prior to the first Sym004 infusions is required. Prior to the implementation of mandatory premedication, 1 serious IRR occurred.

Additional data on the safety and tolerability of Sym004, including data on SAEs, are provided in detail in the IB. Safety information regarding FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, irinotecan) should be referenced from the local packaging inserts.

3.2.4.2 Pharmacokinetics

PK analyses have been performed on patients participating in the Phase 1 trial (Sym004-01) and the Phase 2 trial in patients with SCCHN (Sym004-02). In the Phase 1 trial, serum levels of Sym004 increased in a dose-dependent manner from 0.4 to 12 mg/kg during the dose-escalation phase. Doses of < 3 mg/kg were rapidly cleared from the circulation. A dose-dependent, non-linear increase in serum elimination half-life ($T_{1/2}$) was observed. The geometric mean $T_{1/2}$ was approximately 3 days after doses of 12 mg/kg and 5 days after doses of 18 mg/kg. The 2 antibodies constituting Sym004 displayed similar serum elimination profiles (13, IB).

Data from the Sym004-01 and Sym004-02 trial also documented that the two antibodies constituting Sym004 were present in serum close to a 1:1 ratio at each visit throughout the trial. All of the patients were exposed to detectable levels of Sym004 throughout the dosing periods evaluated. The calculated $T_{1/2}$ increased from the first to the fourth infusion of Sym004, with comparable increases in the calculated Area Under the Concentration-time curve (AUC). The observed increase in exposure was considered to be consistent with down-regulation of the antibody target, the EGFR, after repeated doses of Sym004 (IB).

More complete PK analyses and population PK data are included in the IB.

3.2.4.3 Pharmacodynamic Effects

Tumor and skin biopsies obtained before the first and planned fifth infusions of Sym004 in trial Sym004-01. A decrease in membranous EGFR expression and decreases in the proliferation marker, Ki67, were observed in both tumor and skin biopsies (13). These data provided clinical proof that Sym004 at the doses administered distributed to tumor, inhibited the intended target, and suppressed a known marker of tumor growth.

3.2.4.4 Antitumor Effects

As a part of the Phase 1 Sym004 dose-escalation trial (Sym004-01), antitumor activity was documented in patients with mCRC resistant to anti-EGFR antibody therapy (13). Five of the 39 documented refractory patients (13%) with adequate imaging studies achieved a partial response (PR). These responses were confirmed by independent radiologic review. A PR or disease stabilization, Stable Disease (SD), was documented in 67% of patients with available assessments. An exploratory analysis revealed that the responders to Sym004 were shown to have tumors with WT KRAS, NRAS, and BRAF genotype, as well as having no

evidence of MET amplification. One of the responder's tumors expressed an EGFR mutation (EGFRS492R) at baseline, a marker that is associated with resistance to cetuximab.

3.3 Trial Rationale

Although the use of anti-EGFR mAbs is well established in the treatment of mCRC, only a minority of patients with advanced disease respond to the approved antibodies alone or in combination with chemotherapy (3-8). Patients who do respond initially, ultimately become resistant to combined therapies, including the currently approved anti-EGFR mAbs. The overall magnitude of clinical effects observed with anti-EGFR antibodies alone or in combination has been limited, and patients who develop resistance have few treatment options (3-8). The distinct mechanism of action of Sym004 (9), compared to available anti-EGFR mAbs, as well as the promising nonclinical and clinical data documenting activity in models (9-11) and patients with mCRC refractory to prior anti-EGFR antibody therapy (13), provide strong support for the trial of Sym004 in combination with FOLFIRI therapy in patients with CRC, who have progressed following first-line therapy, but have not received prior therapy with an EGFR inhibitor.

Following treatment with EGFR inhibitors, such as cetuximab and panitumumab, tumors may develop resistance to the treatment. Varieties of trials have documented alterations in tumor cells that may be involved in acquired resistance to anti-EGFR therapies (14). One reported mechanism of resistance is based on increased production of EGFR ligands (15). Sym004 may be able to overcome this resistance mechanism by eliciting a more pronounced down-regulation of the expression of EGFR (9-11,13) than observed with the approved monoclonal anti-EGFR antibodies. This hypothesis is supported by the demonstration of clinical activity in patients considered to be resistant to anti-EGFR mAbs, with an observed response rate after treatment with Sym004 in a range otherwise expected for cetuximab and panitumumab in patients who have not received an anti-EGFR mAb (13).

Based on the above-cited data, this Phase 1b/2a trial is designed to first evaluate the safety and tolerability of Sym004 in combination with FOLFIRI in order to determine the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D). Upon delineation of the RP2D, additional patients who have failed first-line therapy for CRC will receive the combination to assess the antitumor activity of this regimen. The preliminary data suggesting both a different mechanism of action as well as activity of Sym004 in patients with CRC refractory to cetuximab, provides a rationale for improved activity in earlier lines of therapy in patients without acquired resistance to anti-EGFR antibodies.

As of Amendment 3: This amendment to the clinical trial protocol (CTP) is based on a Sponsor decision to discontinue the development of Sym004 in combination with FOLFIRI. As a result, enrollment has stopped and a reduction in the total scope of non-safety related assessments being conducted under this CTP will be implemented.

Patients who are actively being treated with Sym004 alone or in combination with FOLFIRI may continue therapy until unacceptable toxicity or other conditions preventing further administration, progressive disease (PD), or patient's decision to withdraw. Patients no

longer receiving Sym004 alone or in combination with FOLFIRI should be discontinued from study participation. Refer to [Section 7.6](#).

Patients will continue to be followed and assessed for clinical safety-related concerns throughout their respective treatment periods and at minimum for 30 days after the last administration of Sym004.

3.4 Dose Rationale

The starting dose of Sym004 in the trial is based upon prior demonstration that a dose of 12 mg/kg administered weekly was determined to be the RP2D on this schedule although no MTD was formally reached. The safety and tolerability of this dose level on both a weekly and every second week schedules are outlined above and greater detail is available in the IB. In addition, preliminary antitumor activity in patients with mCRC and acquired resistance to available anti-EGFR mAbs was observed after administration of weekly doses of Sym004 of 9 mg/kg or 12 mg/kg (13). Doses of 12 mg/kg and 18 mg/kg have furthermore been tolerated on an every second week schedule (16).

3.5 Overall Benefit/Risk

As previously discussed, Sym004 has been documented to be active in preclinical studies using cetuximab-resistant tumors, as well as in preliminary clinical trials in mCRC and SCCHN patients with acquired resistance to anti-EGFR mAbs (13,17). The activity of Sym004, in patients refractory to therapy with mAbs targeting the EGFR, was similar to the single agent activity seen with these agents in treatment-naïve mCRC patients.

In previous trials, Sym004 showed an acceptable safety profile. The safety profile was similar to that of other anti-EGFR antibodies, although for both skin toxicities and hypomagnesemia the percentage of patients with grade 3 skin toxicities and grade 3/4 hypomagnesemia appeared to be higher (13,17).

The continued unmet need for alternative treatments for mCRC, the available data on the safety, and preliminary data on antitumor activity of Sym004 (13), have been considered in evaluating the risk-benefit relationship in the planning of the trial. Based on the preclinical and clinical data available to date, the conduct of the trial is considered justifiable using the doses and dosage regimens of the IMP as specified in this Clinical Trial Protocol (CTP). In this trial, as applicable, there will be an ongoing assessment of the risk-benefit ratio with periodic evaluation of the results including review by external experts in CRC familiar with the use of anti-EGFR antibodies. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustifiable.

In order to mitigate potential risks, the trial is designed to allow for dose de-escalation if the safety and tolerability of the initial dose exceeds the MTD. If the dose is safe and well tolerated, dose-escalation may proceed to establish a RP2D. The potential to slow infusions, interrupt dosing, decrease the doses administered, and to discontinue administration of

Sym004 in the event of specific AEs are outlined. In addition, steps to prevent infusion reactions and measures to intervene in the event of electrolyte imbalances and cutaneous toxicities are specified. Furthermore, prophylactic treatment for FOLFIRI induced diarrhea and vomiting according to institutional standards is required.

The trial will be conducted in accordance with the CTP, the principles of the Declaration of Helsinki (18), ICH E6 GCP (1), and other laws in the countries where the trial takes place.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 Dose-Escalation (Phase 1b)

As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, the primary, secondary, and exploratory objectives are no longer applicable. Clinical safety-related evaluations will continue to be conducted.

4.1.1 Primary Objective

To determine the MTD and/or RP2D of Sym004 when administered by iv infusion every second week in combination with a standard dosing regimen of FOLFIRI (Folinic Acid [FA; leucovorin], 5-fluorouracil [5-FU], irinotecan) to patients with locally advanced or metastatic CRC.

4.1.2 Secondary Objectives

- To determine the safety and tolerability of Sym004 when administered in combination with a standard dosing regimen of FOLFIRI
- Evaluation of the immunogenicity of Sym004
- Characterization of the PK profile of Sym004
- Preliminary evaluation of the antineoplastic effect of Sym004 plus FOLFIRI as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) ([Appendix 1](#))

4.2 Dose-Expansion (Phase 2a)

4.2.1 Primary Objective

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

4.2.2 Secondary Objectives

- Further evaluation of the safety and tolerability of Sym004 when administered at the RP2D in combination with FOLFIRI
- Continued evaluation of the immunogenicity of Sym004

4.3 Exploratory Studies

- Evaluation of the utility of pharmacodynamic biomarkers of Sym004 action, and estimation, if feasible, of the magnitude and duration of biological activity.

4.4 Trial Endpoints

As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, only the clinical safety-related evaluations will continue to be conducted.

4.4.1 Primary Endpoint of Dose-Escalation (Phase 1b)

The primary endpoint of the dose-escalation phase is the occurrence of Dose-Limiting Toxicities (DLT) observed during Cycle 1 of Sym004 administration in combination with FOLFIRI.

4.4.2 Primary Endpoint of Dose-Expansion Phase (Phase 2a)

The primary endpoint of the dose-expansion phase is confirmed objective antitumor response.

4.4.3 Secondary Endpoints of Dose-Escalation and Dose-Expansion Phases

4.4.3.1 Safety

- Nature, incidence and severity of AEs measured from baseline to end of trial participation

NOTE: Adverse Events are graded by the Investigator according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4.03, in the following referred to as CTCAE)

- AEs leading to dose-reductions, dose delays and permanent treatment cessation
- Changes in safety laboratory values from baseline to end of trial participation
- Changes in vital signs and physical examinations from baseline to end of trial participation
- Occurrence of anti-drug antibodies (ADA) to Sym004 measured in serum at selected timepoints from baseline to end of trial participation

4.4.3.2 Anti-tumor Response

- Documented Objective Response (OR), defined as documented Partial Response (PR) or Complete Response (CR)
- Duration of OR from time of first PR or CR to progressive disease (PD)
- Changes in sum of diameters of target lesions from baseline to end of trial participation
- Stable Disease (SD) for > 4 months
- Time to documented disease progression, death, patient withdrawal or end of trial participation, whichever comes first

4.4.3.3 Pharmacokinetic Assessment (Dose-Escalation only)

- PK endpoints, derived from the concentration-time curves of Sym004, mAb992 and mAb1024, respectively after the first and fourth infusion of Sym004:

$AUC_{Norm, 0-336h}$ Dose-normalized area under the concentration-time curve from End of Infusion (EOI) to 336 hours

AUC_{0-336h} Area under the concentration-time curve from EOI to 336 hours

C_{max} Maximum concentration

T_{max} Time to reach maximum concentration

C_{trough} Trough concentration

$T_{1/2}$ Elimination half-life

CL Clearance

V Volume of distribution

4.4.3.4 Pharmacodynamic and Biomarker Assessment

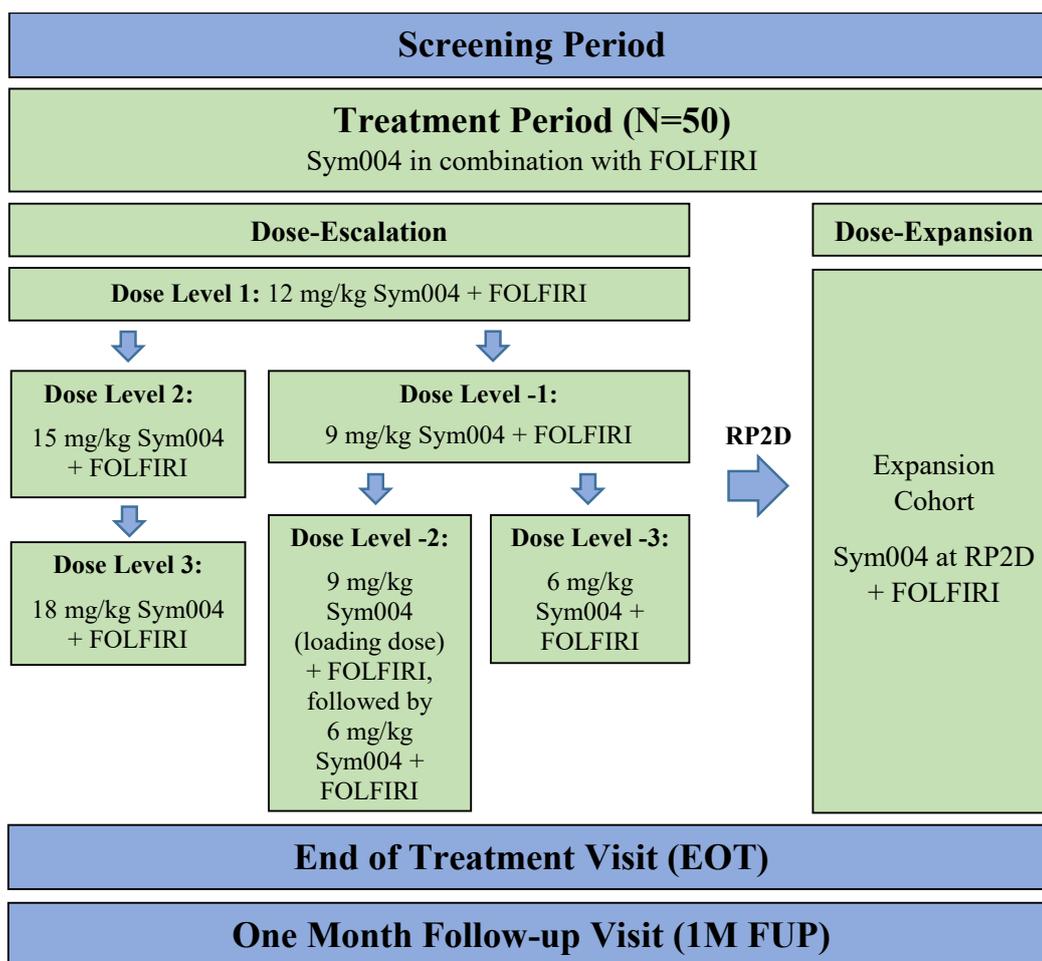
- Urine and peripheral blood collection for assessment of biomarkers related to the EGFR pathway
- Other potential biomarkers to be determined (i.e. genes, gene transcripts and proteins of the receptor tyrosine kinases (RTKs))

5 TRIAL DESIGN

5.1 Overall Design and Plan

This is an open-label, multicenter, phase 1b/2a trial with an initial dose-escalation phase followed by a dose-expansion phase. The trial design is shown in Figure 1.

Figure 1 Overall Trial Design



Abbreviations: N, number of patients; RP2D, Recommended Phase 2 Dose

The trial will be conducted in USA and countries within the EU.

Approximately 8 investigational trial sites, hereafter called “trial sites”, will participate in the dose-escalation phase to determine MTD, safety and tolerability of multiple dose levels of Sym004 administered every second week in combination with a standard dosing regimen of FOLFIRI. Patients will be allocated in sequence to 1 of up to 5 dose levels of Sym004, based on tolerability. The RP2D will be based on the MTD evaluation as well as other toxicities observed in the study, and may include tolerability observed in Cycle 1 and subsequent

cycles as well as PK and other data. The MTD and RP2D may or may not be the same, and the RP2D may be selected based on overall tolerability without defining the MTD.

Approximately 10 to 15 trial sites will participate in the dose-expansion phase to investigate the antitumor activity of Sym004 at the RP2D determined in combination with FOLFIRI and to further assess the safety and pharmacodynamics effects of this regimen.

Screening Period: After providing informed consent, the eligibility of patients will be established according to the protocol-defined inclusion and exclusion criteria ([Section 6.1](#) and [Section 6.2](#), respectively). Once all screening procedures have been completed and eligibility has been confirmed, a blood and urine sample will be taken for biomarker analysis. Furthermore, if an archived tumor tissue biopsy sample for central evaluation of biomarkers and Rat Sarcoma (RAS) mutations (KRAS and NRAS, exons 2, 3, and 4) is not available, the patient will have a tumor biopsy taken.

Eligible patients will be enrolled into the trial and enter the treatment period.

Treatment Period: During the dose-escalation phase, patients will be assigned consecutively to the next available open treatment cohort and the dose of Sym004 to be administered will be confirmed in writing by Sponsor or designee on an allocation form. Full details of the dosing regimens for Sym004 are provided in [Section 7.1.4](#). Once the RP2D has been identified, all subsequent patients will be enrolled into the dose-expansion cohort and will receive the RP2D dose of Sym004 in combination with FOLFIRI.

Patients in the trial will receive iv infusions every second week of Sym004 in combination with a standard dosing regimen of FOLFIRI ([Section 7.2.1](#)) until occurrence of any of the following: Unacceptable toxicity or other conditions preventing further administration, PD, termination of the trial, or patient's decision to withdraw. Patients may discontinue treatment (Sym004 and FOLFIRI) simultaneously; may discontinue Sym004 before discontinuing FOLFIRI; or may discontinue FOLFIRI before discontinuing Sym004.

The visit schedule for the treatment period will apply until both Sym004 and FOLFIRI have been discontinued ([Table 2](#)).

As of Amendment 3: The visit schedule for the treatment period will apply until Sym004 has been discontinued.

End of Treatment/Follow-up: Once both Sym004 and FOLFIRI have been discontinued, an End of Treatment (EOT) Visit will be performed within 10 days from the decision to withdraw treatment.

A follow-up visit will be performed 1 month after the last administration of Sym004/FOLFIRI (i.e. only after both treatments have been discontinued). This One Month Follow-up (1M FUP) visit will constitute the end of trial participation for the patient.

As of Amendment 3: Once Sym004 has been discontinued, an EOT Visit will be performed within 10 days from the decision to withdraw treatment, and a follow-up visit will be performed 1 month after the last administration of Sym004.

5.2 Discussion of Trial Design

5.2.1 Rationale for Trial Design

FOLFIRI is a standard chemotherapeutic regimen used in the treatment of patients with mCRC in either the first- or second-line settings. Cetuximab, a chimeric antibody targeting the EGFR, had modest single agent activity in patients with advanced CRC, but increased efficacy was observed when combined with standard combination chemotherapy regimens used to treat this malignancy. Similar data are available for panitumumab, a human mAb targeting the EGFR. Given the activity and novel mode of action of Sym004 demonstrated in nonclinical studies and as single agent in early phase clinical trials, further clinical trials are warranted to explore Sym004 in combination with regimens commonly utilized in the treatment of CRC patients.

5.2.2 Rationale for Trial Population

Antibodies to EGFR have been approved alone and in combination with chemotherapy for the treatment of patients with CRC. The agents are active in only a subset of patients and resistance develops in those who respond initially. Sym004 has been shown to have activity in patients refractory to therapy with anti-EGFR antibodies in prior clinical trials (13,17), thus further trials in CRC patients who have not received prior anti-EGFR therapy are warranted.

5.2.3 Rationale for Starting Dose and Route of Administration

The rationale for the starting dose, route of administration and duration of infusion is based upon the safety and tolerability of Sym004 documented in completed and ongoing trials. Intravenous dosing with Sym004 was utilized in nonclinical toxicology studies, and in prior trials of Sym004. Intravenous dosing is the route utilized for the majority of mAbs used in the treatment of patients with malignancies including previously approved mAbs to EGFR. The starting dose of 12 mg/kg is based upon the safety and tolerability of this dose level administered every week or every second week.

5.2.4 Rationale for Dose-Escalation and Dose-Expansion

The dose-escalation (or de-escalation) in cohorts is based on prior experience with Sym004 in Phase 1 and 2 completed and ongoing trials. The standard 3 + 3 design is being used to determine safety and tolerability within cohorts and to make decisions regarding the dose assigned to the next group. The dose expansion group will provide information on the antitumor activity as well as additional information on the safety and tolerability of the combination of Sym004 and FOLFIRI. These data will facilitate decision-making with regard to the implementation of future trials of Sym004 in patients with CRC.

5.3 Schedule of Events

The overall trial plan is introduced in [Table 1](#) and further defined in the below sections.

Table 1 Overall Trial Plan

Screening Period	
Screening	14 days within first dose of Sym004 + FOLFIRI
Treatment Period	
Treatment Allocation	The allocated dose of Sym004 will depend upon cohort assignment of Sym004 and will be confirmed by the Sponsor or designee on an allocation form FOLFIRI is given as a standard dosing regimen to all patients
Sym004 + FOLFIRI	The trial treatments will consist of Sym004 in combination with FOLFIRI. Sym004 and FOLFIRI are both initiated on C1/D1 and will be administered every second week by iv infusion (Day 1 and Day 15 of each 28 day cycle [± 2 days]). The Sym004 infusion will be delivered first. The FOLFIRI regimen administration will commence no sooner than 1 hour following completion of Sym004 administration.
Discontinuation of Sym004 and/or FOLFIRI*	Treatment will continue in cycles of 28 days (± 2 days) until unacceptable toxicity or other conditions preventing further treatment, PD, termination of the trial or patient's decision to withdraw. Sym004 and FOLFIRI may be discontinued simultaneously or one may be discontinued before the other. The schedule for the treatment period will apply from the initiation of Sym004 and FOLFIRI until <u>both</u> Sym004 <u>and</u> FOLFIRI have been discontinued.
End of Treatment	
End of Treatment (EOT)*	Within 10 days after the decision to discontinue Sym004 and FOLFIRI (or the last of the two), an EOT Visit must be performed
Follow-up	
One Month Follow-up (1M FUP)*	Follow-up continues until 1 month (28 + 7 days) after the last dose of Sym004/FOLFIRI. At that time, a 1M FUP Visit must be performed. This 1M FUP visit constitutes the end of trial participation for the patient.

Abbreviations (in alphabetical order): C1/D1, Day 1 of Cycle 1; EOT, End of trial treatment Visit (Sym004 and FOLFIRI); 1M FUP, One Month Follow-up Visit

***As of Amendment 3:** The schedule for the treatment period will apply from the initiation of Sym004 and FOLFIRI until Sym004 has been discontinued. An EOT Visit will be performed within 10 days from the decision to withdraw treatment with Sym004, and a follow-up visit will be performed 1 month after the last administration of Sym004.

5.3.1 Screening

When the trial site identifies a patient suitable for screening, the Sponsor or designee should be contacted to ensure that a cohort is open for inclusion. Once confirmed, the patient may be approached for informed consent. Screening activities may begin only once written informed consent has been obtained.

All patients giving informed consent to participate in the trial will receive a unique patient number. This number is composed of a four-digit prefix, which identifies the site, and a three-digit number, allocated sequentially starting from 001 for the first patient screened at the site, 002 for the second patient screened etc.

The trial site staff must complete an allocation form, stating at minimum the allocated patient number and date of birth, along with the planned dates of screening and the day of first scheduled Sym004 and FOLFIRI administration (Cycle 1/Day 1, in the following C1/D1). The planned date of C1/D1 will need to be agreed upon in collaboration with the Sponsor or designee for the dose-escalation cohorts, in order to ensure adequate time between dosing of the first patient and dosing of subsequent patients in each cohort. The completed allocation form will then be sent to the Sponsor or designee prior to or on the day of Screening.

All screening activities must be performed within 14 days prior to C1/D1, unless otherwise specified. A Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) performed within 28 days prior to C1/D1 may be used for evaluation of eligibility, provided that the scan has been performed according to protocol requirements. In the event a tumor biopsy is required for eligibility, informed consent may be obtained outside the 14-day screening period prior to C1/D1 to allow adequate turnaround time for receipt of results.

Individual screening assessments may be repeated prior to C1/D1, if justified and documented by the Investigator.

Once eligibility has been confirmed in accordance with the inclusion and exclusion criteria, the allocation form will be fully completed and signed by the Investigator and resent to the Sponsor or designee. A copy of the fully executed allocation form will be returned to the trial site for archiving. This form documents the allocated dose of Sym004.

5.3.2 Screening-Failures

A patient found not eligible for the trial after giving informed consent is considered a screening-failure. The allocation form must be completed and sent to the Sponsor or designee to confirm the outcome of the screening process.

Re-screening of a patient is allowed.

5.3.3 Treatment

On the day of the first scheduled Sym004 infusion, C1/D1, and prior to the start of infusion (SOI), the Investigator must assess whether any changes have occurred in the clinical state of the patient since screening which would exclude the patient from the trial.

The trial treatment will consist of Sym004 in combination with FOLFIRI. Both therapies will be administered every second week by iv infusion (Day 1 and Day 15 of each 28 day cycle, \pm 2 days). Sym004 will be administered first, followed by FOLFIRI, with a minimum interval of 1 hour between Sym004 End of Infusion (EOI) and FOLFIRI SOI.

The dose of Sym004 to be administered will be according to the cohort to which the patient is allocated and will be documented on an allocation form.

There will be no intra-patient dose-escalation.

In the event of toxicity due to Sym004, FOLFIRI or the Sym004/FOLFIRI combination, the dose of either Sym004 or a component of the FOLFIRI regimen may be reduced, as described in [Section 7.1.5](#) and [7.2.1.1](#).

Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, PD, termination of the trial, or patient's decision to withdraw.

An individual patient may discontinue treatments (Sym004 and FOLFIRI) simultaneously; may discontinue Sym004 treatment before discontinuing FOLFIRI; or may discontinue FOLFIRI before discontinuing Sym004 treatment.

The visit schedule for the treatment period will apply until both Sym004 and all components of FOLFIRI have been discontinued.

As of Amendment 3: The visit schedule for the treatment period will apply until Sym004 has been discontinued.

5.3.4 End of Treatment and One Month Follow-up Visit

An EOT Visit will be performed for all patients within 10 days after the decision to discontinue treatment with all trial medications (i.e. only once both Sym004 and FOLFIRI have been discontinued).

The patient will return for follow-up 1 month (28+7 days) after the last dose of Sym004/FOLFIRI, whichever is last (i.e. only once both Sym004 and FOLFIRI have been discontinued). This will be the 1M FUP Visit.

As of Amendment 3: An EOT Visit will be performed for all patients within 10 days after the decision to discontinue treatment with Sym004. The patient will return for follow-up 1 month after the last administration of Sym004.

5.3.5 Flow Chart – Schedule of Assessments

A complete schedule of assessments is provided in the trial flow chart in [Table 2](#).

All efforts should be made to perform assessments as close as possible to the scheduled time points. Visit windows are included in the flow chart.

Table 2 Flow Chart – Schedule of Assessments

Pre-Treatment Phase		Treatment Phase ¹								Post-Treatment Phase	
Cycle Number	Screening	Cycle 1				Cycle 2, 4, 6 etc.		Cycle 3, 5, 7 etc.		EOT	1M FUP
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D8 (±2)	D15 (±2)	D22 (±2)	D1	D15 (±2)	D1	D15 (±2)	≤ 10 d from the decision of trial treatment withdrawal	1 month after last dose of trial treatment (28+7d)
Informed Consent	X										
Baseline Characteristics/Eligibility ²	X	X									
Safety Assessments											
Medication Survey	X	X	X	X	X	X	X	X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation (dose-escalation only) ³		X	X	X	X	C2/D1					
Vital Signs and Body Weight	X	X		X		X	X	X	X	X	X
ECOG PS	X	X				X		X		X	X
Physical Examination	X	X				X		X		X	X
Dermatological Examination	X	X		X		X	X	X	X	X	X
ECG ⁴	X									X	
Safety blood samples ⁵	X	X	X	X	X	X	X	X	X	X	X
Urinalysis ⁵	X	X		X		X		X		X	X
Pregnancy Test	X									X	
Disease Assessments											
(Archival) Tumor Biopsy Collection ^{6,7}	X										
Tumor Marker Evaluation ⁸	X						End of C			X	X
Disease Status Evaluation by CT/ MRI ^{9,10}	X						End of C			X	X
*Additional Assessments											
*PK Samples (dose-escalation only) ¹¹		X		X		X	X	X		X	X
*ADA Sample		X						X		X	X
*Biomarker Blood and Urine Sample ¹²	X						End of C2			X	
Trial Treatment											
Skin Toxicity Prophylaxis and TX ¹³		X	X	X	X	X	X	X	X	X	X
Infusion Reaction Prophylaxis ¹⁴		X		X							
Sym004 Infusion		X		X		X	X	X	X		
Gastrointestinal Toxicity Prophylaxis ¹⁵		X		X		X	X	X	X		
FOLFIRI Infusion		X		X		X	X	X	X		
Post-Infusion Monitoring		X		X		X	X	X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, Cycle; CT, computed tomography scan; D/d, day(s); DLT, dose-limiting toxicity; EOT, End of trial treatment Visit (Sym004 and FOLFIRI); ECG, electrocardiography; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; 1M FUP, One Month Follow-up Visit; PK, pharmacokinetic; (S)AE, (serious) adverse event; TX, therapy

*Omitted with Amendment 3

- 1) The treatment phase continues until the patient is withdrawn from Sym004 (**As of Amendment 3**)
- 2) Screening assessments include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment etc.
- 3) **Applicable for dose-escalation only:** DLTs are reported during Cycle 1 with final assessment on scheduled first day of Cycle 2, prior to dosing
- 4) In addition to the scheduled ECGs, an ECG should be performed in the event of \geq Grade 3 hypomagnesemia and if otherwise clinically indicated. Furthermore, in the event of QT prolongation, an ECG is to be performed prior to the next dose of Sym004
- 5) Local laboratory results must be available and assessed no later than 2 days prior to each Sym004/FOLFIRI infusion. Refer to [Table 16](#) for further details
- 6) Sample is to be taken only after patient eligibility has been confirmed
- 7) A tumor biopsy must be performed, if archived tumor tissue is not available for central evaluation of biomarkers, RAS mutations (KRAS and NRAS, exon 2, 3, 4).
- 8) Tumor Marker, Carcinoembryonic Antigen (CEA), completed at EOT if $>$ 3 weeks since previous evaluation; at 1M FUP (if PD was not documented before or at EOT)
- 9) CT or MRI imaging schedule and conditions, applying to all cohorts:
 - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle.
 - In the event of suspected PD, a CT/MRI is to be performed as soon as possible
 - In the event of CR/PR, a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR
- 10) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed $>$ 3 weeks before; a CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents disease progression before or at EOT
- 11) ***Applicable for dose-escalation only:** Extended PK sampling for PK profiling will be done for Day 1 (C1/D1) and in relation to the 4th Sym004 infusion (scheduled for C2/D15). For all other visits with PK sampling, blood samples are taken prior to and at the end of each infusion. Refer to [Table 17](#) for further details
- 12) ***A biomarker blood and urine sample is taken during screening after patient eligibility has been confirmed. Sampling is repeated at the end of Cycle 2, or upon PD whichever occurs first, and at EOT**
- 13) Prophylactic treatment with an oral antibiotic and a topical steroid until end of Cycle 2 followed by comprehensive treatment of skin toxicities
- 14) Prior to the first 2 infusions with Sym004 patients will receive glucocorticoid therapy and an antihistamine. For infusion following Cycle 1, pre-medication is at the Investigators discretion
- 15) Patients will receive prophylactic treatment for nausea and vomiting according to institutional standards, and all patients will be treated with loperamide in an effort to prevent diarrhea during Cycle 1. Prophylaxis with loperamide may be continued beyond Cycle 1 at the Investigator's discretion.

***Omitted with Amendment 3**

5.4 Recruitment Period

The dose-escalation phase of the trial is expected to begin Q4 2015. Patients will be sequentially enrolled to dose-escalation cohorts until selection of the RP2D, expected by Q4 2016.

The dose-expansion phase of the trial is expected to begin Q4 2016 with enrollment to be completed Q2-Q3 2017.

5.5 Number of Patients

In total, 50* patients are planned to be treated with Sym004 in combination with FOLFIRI.

The number of patients treated during the dose-escalation phase will depend upon the observed tolerability of Sym004 in combination with FOLFIRI. Up to approximately 18 patients are expected to be treated during the dose-escalation phase. Enrollment in the dose-expansion phase will continue until a total of 50 patients have been enrolled in dose-escalation and dose-expansion phases combined.

For details regarding the sample size considerations please refer to [Section 10.1](#).

*As of Amendment 3: Accrual to this trial has stopped and the total planned number of patients will not be enrolled.

5.6 End of Trial

The end of trial will be reached at the latest 1 month (28 +7 days) after the last patient has been withdrawn from trial treatments.

5.7 Independent Evaluation Committees

An Independent Safety Monitoring Committee (ISMC) will be established for the trial. The composition and role of the ISMC is described in [Section 12.1](#).

6 PATIENT SELECTION AND WITHDRAWAL

Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor or designee prior to enrollment.

6.1 Inclusion Criteria All Cohorts

For inclusion in the trial, all of the following criteria must be fulfilled:

1. Written informed consent given before any trial-specific procedure
2. Male or female, at least 18 years of age at the time of informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
4. Life expectancy > 3 months assessed during Screening
5. Histologically or cytologically confirmed, locally advanced or metastatic CRC that is documented to be without KRAS or NRAS gene mutations (i.e. tumors must express the KRAS and NRAS wild type (WT), exon 2, 3 and 4).
6. Failed* prior adjuvant therapy or prior therapy for treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab.

*Failure is defined as radiologic progression

7. Eligible for FOLFIRI
8. Archival tumor tissue available for confirmation of RAS mutation evaluation. If tumor tissue is not available, patients must be willing to undergo a tumor biopsy and must have a tumor that is safely accessible for biopsy
9. Measurable disease according to RECIST v1.1 ([Appendix 1](#))

NOTE: Measurable disease is defined as 1 or more target lesions assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). A tumor lesion situated in a previously irradiated area is considered measurable only if subsequent disease progression has been documented in the lesion

10. Disease that is currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor
11. If female and of childbearing potential, a negative pregnancy test
12. Not of childbearing potential or agrees to use a medically effective method, as per institutional standards, of contraception during the trial and for 3 months after the last dose of trial drug

6.2 Exclusion Criteria All Cohorts

Patients meeting any of the following criteria will not be permitted to enter the trial:

1. Prior therapy with anti-EGFR antibodies, anti-EGFR small molecule inhibitors or irinotecan (CPT-11)
2. Any antineoplastic agent (standard or investigational) within 4 weeks prior to C1/D1
3. Radiotherapy against target lesions within 4 weeks prior to C1/D1

NOTE: Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function
4. Discontinuation of prior therapy with oxaliplatin and a fluoropyrimidine due to diarrhea \geq Grade 3
5. Immunosuppressive or systemic hormonal therapy within 2 weeks prior to C1/D1 with the exception of the following allowed therapies:
 - a. Hormonal therapy (e.g., Megace) for appetite stimulation
 - b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
 - c. Oral replacement glucocorticoid therapy for adrenal insufficiency
 - d. Low-dose maintenance steroid/hormonal therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation)
 - e. Hormonal contraceptive therapy
6. Prophylactic use of hematopoietic growth factors within 1 week prior to C1/D1
7. Active second malignancy or history of another malignancy within the last 5 years, with the exception of:
 - a. Treated, non-melanoma skin cancers
 - b. Treated carcinoma in situ of the breast or cervix
 - c. Controlled, superficial carcinoma of the urinary bladder
 - d. T1a or b carcinoma of the prostate treated according to local standard of care, with Prostate-Specific Antigen (PSA) within normal limits for the institution
8. Known Central Nervous System (CNS) or leptomeningeal metastases not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required

NOTE: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids or anticonvulsants, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed at least 4 weeks apart with the most recent study performed within 12 weeks prior to first trial drug administration
9. Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy

NOTE: Patients with any persistent chronic toxicity of Grade 1 in severity, and persistent Grade 2 alopecia and/or neuropathy secondary to prior oxaliplatin therapy, will be considered eligible for enrollment

10. Major surgical procedure within 4 weeks prior to C1/D1 or inadequate recovery from any prior surgical procedure
11. Non-healing wounds on any part of the body
12. Patients with underlying conditions which may affect or be affected by the administration of agents in the FOLFIRI regimen. This includes
 - a. Gilbert-Meulengracht syndrome
 - b. Dihydropyrimidine dehydrogenase deficiency
13. Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 4 weeks prior to C1/D1; any prior thrombosis must be adequately treated and stable
14. Active uncontrolled bleeding or a known bleeding diathesis
15. Significant gastrointestinal abnormalities, including:
 - a. History of inflammatory bowel disease
 - b. Diarrhea \geq Grade 2 within 2 weeks prior to C1/D1
 - c. Requirement for intravenous alimentation
 - d. Prior surgical procedures affecting absorption
 - e. Active peptic ulcer disease
16. Patients with a significant cardiovascular disease or condition, including:
 - a. Congestive heart failure (CHF) currently requiring therapy
 - b. Class III or IV cardiovascular disease according to the New York Heart Association's (NYHA) Functional Criteria (19)
 - c. Need for antiarrhythmic medical therapy for a ventricular arrhythmia
 - d. Severe conduction disturbance (e.g., 3rd degree heart block)
 - e. Unstable angina pectoris (last episode at least 6 months prior to C1/D1)
 - f. Uncontrolled hypertension (per the Investigator's discretion)
 - g. Myocardial infarction within 6 months prior to C1/D1
17. Abnormal hematologic, renal or hepatic function as defined by the following criteria:

- a. Absolute neutrophil count (ANC) $< 1.5 \times 10^9/L$ ($1500/mm^3$)
- b. Hemoglobin ≤ 9 g/dL
- c. Platelet count $< 100 \times 10^9/L$ ($100,000/mm^3$)
- d. Serum creatinine $> 1.5 \times$ upper limit of normal (ULN) for the institution
- e. Aspartate aminotransferase (AST) $> 5 \times$ ULN for the institution
- f. Alanine aminotransferase (ALT) $> 5 \times$ ULN for the institution
- g. Total bilirubin $> 1.5 \times$ ULN for the institution
- h. Prothrombin Time (PT) as assessed by International Normalized Ratio (INR) $> 1.5 \times$ ULN for the institution
- i. Partial Thromboplastin Time (PTT) $> 1.5 \times$ ULN for the institution
18. Known history of Human Immunodeficiency Virus (HIV) infection
19. Known active hepatitis B or C virus infection
20. Any of the following within 2 weeks prior to C1/D1:
 - a. Any serious or uncontrolled infection
 - b. Any infection requiring parenteral antibiotics
 - c. Unexplained fever > 38.0 °C
21. Known or suspected hypersensitivity to any of the excipients of the Sym004 drug product
22. Any other life-threatening illness, significant organ system dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with the evaluation of the safety of the trial drug
23. Any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with trial procedures or is unwilling or unable to comply with trial requirements at the discretion of the Investigator
24. Breast feeding, or plans by the patient (or the patient's partner) to become pregnant during treatment or within 3 months after the end of treatment

6.3 Withdrawal from Trial Treatment

Sym004 and FOLFIRI may be discontinued simultaneously; Sym004 treatment may be discontinued before discontinuing FOLFIRI; or FOLFIRI may be discontinued before discontinuing Sym004 treatment.

Further, if 5-FU/FA treatment is discontinued, irinotecan/Sym004 may be administered. If irinotecan administration is discontinued, 5-FU/FA/Sym004 administration may be continued.

The visit schedule for the treatment period will apply until Sym004 and all components of FOLFIRI have been discontinued. Once this has occurred, an EOT Visit will be performed within 10 days after the decision to discontinue the last of the two; Sym004 and/or FOLFIRI.

After EOT, the patient will continue to be followed until 1 month (28 +7 days) after the last dose of Sym004/FOLFIRI, when the 1M FUP Visit must be completed.

As of Amendment 3: The visit schedule for the treatment period will apply until Sym004 has been discontinued. An EOT Visit will be performed within 10 days from the decision to withdraw treatment with Sym004, and a follow-up visit will be performed 1 month after the last administration of Sym004.

6.3.1 Withdrawal from Treatment with Sym004 and/or FOLFIRI

The patient must be withdrawn from treatment with Sym004 and/or FOLFIRI in the event of any of the following:

- A DLT considered by the Investigator to require treatment discontinuation (See [Section 9.5](#)) (dose-escalation cohorts only)
- Occurrence of an AE considered by the Investigator to require treatment discontinuation
- CTCAE Grade 4 skin toxicity (applies to Sym004 only)
- FOLFIRI-related toxicity not controlled by dose-reduction guidelines are outlined in [Table 7](#) in [Section 7.2.1.1](#) and [Appendix 2](#)
- PD, verified by CT/MRI according to RECIST v1.1 ([Appendix 1](#))
- Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation
- Requirement for a significant surgical procedure

NOTE: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor or designee. A brief interruption in therapy may be considered
- An intercurrent illness which, in the opinion of the Investigator, would prevent completion of trial-related evaluations
- The Investigator judges it necessary due to medical reasons
- Use of prohibited concomitant medication, as defined in [Section 7.5.2](#)
- Pregnancy

- Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and may be discontinued from treatment after discussion with the Sponsor
- Noncompliance with trial procedures may require discontinuation after discussion with the Sponsor
- Patient withdrawal of consent and election to discontinue treatment. (Patients may leave the trial at any time for any reason if they wish to do so, without any consequences)
- Termination of the trial by the Sponsor

6.3.2 Withdrawal from Trial

The patient must be withdrawn from trial in the event of any of the following:

- The patient withdraws consent to participate
- The Investigator judges it necessary due to medical reasons

The EOT and the 1M FUP visits should be performed to the extent possible and the Investigator should ensure any SAE is followed as described in [Section 9.3](#).

6.4 Replacement of Patients

6.4.1 Dose-Escalation Phase

Patients who do not complete Cycle 1 as defined in [Section 9.5.2](#), for reasons other than DLTs, can be replaced.

Data from these patients will be included in the safety analysis, but will not contribute to the determination of the MTD.

6.4.2 Dose-Expansion Phase

It is not planned to replace any patients in the dose-expansion phase.

7.1.4 Administration of Sym004

7.1.4.1 Treatment Schedule

This is a non-randomized, open-label trial. All patients will be allocated to the IMP, Sym004, in combination with FOLFIRI. The dose of Sym004 will vary depending upon cohort assignment.

All patients will be given iv infusions of Sym004, administered every second week (Day 1 and Day 15 of each 28 day cycle ± 2 days) through a peripheral line or indwelling catheter, and with the use of an infusion pump and an inline filter.

Sym004 is dosed according to the body weight. The allocated dose level will be confirmed in writing by Sponsor or designee on the allocation form.

For all Sym004 infusions, a complete dosing history will be recorded, i.e.:

- Total dose and volume administered
- Start and stop time of infusion
- Infusion interruption or termination and reason for such actions

7.1.4.2 Dose-Escalation Phase

During the dose-escalation phase of the trial, the following dose levels of Sym004 will potentially be evaluated in combination with FOLFIRI:

- Dose Level 1: Sym004 12 mg/kg + FOLFIRI
- Dose Level 2: Sym004 15 mg/kg + FOLFIRI
- Dose Level 3: Sym004 18 mg/kg + FOLFIRI

If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, successive lower dose levels will be explored:

- Dose Level -1: Sym004 9 mg/kg + FOLFIRI
- Dose Level -2: Sym004 9 mg/kg (loading dose) + FOLFIRI followed by 6 mg/kg + FOLFIRI
- Dose Level -3: Sym004 6 mg/kg + FOLFIRI

If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) has not exceeded the MTD and is well tolerated during Cycle 1, but overall tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose Level -2 may be explored.

If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) during Cycle 1 has not exceeded the MTD, but tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose-Level -3 may be explored.

If the toxicity profile of lower doses where mandatory diarrhea prophylaxis is utilized indicates that the dose is well tolerated, further evaluation of Dose Level 1, and potentially Dose Levels 2 and 3 may take place after approval by the ISMC.

Cohorts will be filled sequentially. Patients will be allocated to the next available treatment slot within the current or next cohort, as appropriate and depending on the ongoing observation of DLTs and other safety parameters.

7.1.4.3 Dose-Escalation Decision Points

In the dose-escalation 3 + 3 design, at least 3 patients will be treated per dose level.

Enrollment will be staggered between the first and second patient in each new cohort. The first patient in a 3-patient cohort must have completed and tolerated Cycle 1 (at minimum 2 full doses of both Sym004 and FOLFIRI plus 14 days of follow-up [± 2 days]) in order to allow for review of clinical and laboratory assessments. Thereafter patients within a cohort may be added concurrently.

Progression from a current dose level to the next, will only proceed following evaluation of tolerability at the current dose level. Thus, dosing of the first patient at Dose Level 2 will commence only once Dose Level 1 has been found to be tolerable, and dosing in Dose Level 3 will only commence once Dose Level 2 has been found to be tolerable according to the dose-escalation decision points below:

- If no DLTs are encountered in any of the first 3 patients completing Cycle 1 within a dose level, dose-escalation may continue to the next level
- If 1 of 3 patients within a dose level experiences a DLT, 3 more patients will be enrolled at the same dose level. If no DLTs are encountered in the 3 additional patients, dose-escalation may continue to the next level when all patients have completed Cycle 1
- If ≥ 2 patients within a dose level (of up to 6 patients) experience a DLT, then that dose will be considered to have exceeded the MTD and the dose level just below this dose level will be considered to be the MTD

NOTE: Should ≥ 2 of 6 patients at Dose Level 1 experience a DLT, then the dose will be reduced to Dose Level -1. Furthermore, if ≥ 2 of 6 patients at Dose Level -1 experience a DLT, then the dose will be reduced to Dose Level -3.

- Once the ISMC declares the potential MTD, this MTD dose level will be completed to a total of 6 patients, if not already done. In order to confirm the MTD, ≤ 1 patient of 6 within the dose level may have experienced a DLT
- If no DLT's are encountered in any of the first 3 patients at Dose Level 3, 3 more patients will be enrolled at this dose level. If ≤ 1 patient experiences a DLT, dose-escalation will end without formally having reached the MTD. The ISMC will together with the Sponsor declare the RP2D based on the available safety data

Each patient enrolled will receive doses of Sym004 at the allocated dose, unless dose-reduction is necessary as specified in [Section 7.1.5](#). There will be no intra-patient dose-escalation.

7.1.4.4 Dose-Expansion Phase

Once the RP2D has been determined during the dose-escalation phase, the enrollment into the dose-expansion phase will commence. All patients enrolled to this phase will be treated at the established RP2D of Sym004 in combination with FOLFIRI.

7.1.4.5 Infusion Rate for Administration of Sym004

For the first 2 Sym004 infusions (Cycle 1), the infusion rate should be increased every 30 minutes to a maximum of 400mL per hour according to the schedule shown in [Table 4](#). Thus, a maximum of 19.2 mg Sym004 will be delivered per minute per kg body weight (based on an 80 kg patient).

Table 4 Infusion Rate for Administration of Sym004

	Dose Level 4.5 mg/kg			
	Volume 250 mL, body weight 80 kg, 1.4 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	72	2.4
31-60	150	75	108	3.6
61-90	250	125	180	6.0
Total		250 mL		

	Dose Level 6 mg/kg			
	Volume 250 mL, body weight 80 kg, 1.9 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	96	3.2
31-60	150	75	144	4.8
61-90	250	125	240	8.0
Total		250 mL		

	Dose Level 9 mg/kg			
	Volume 500 mL, body weight 80 kg, 1.4 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	72	2.4
31-60	200	100	144	4.8
61-90	300	150	216	7.2
91-120	400	200	288	9.6
Total		500 mL		

	Dose Level 12 mg/kg			
	Volume 500 mL, body weight 80 kg, 1.9 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	96	3.2
31-60	200	100	192	6.4
61-90	300	150	288	9.6
91-120	400	200	384	12.8
Total		500 mL		

	Dose Level 15 mg/kg			
	Volume 500 mL, body weight 80 kg, 2.4 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	120	4.0
31-60	200	100	240	8.0
61-90	300	150	360	12.0
91-120	400	200	480	16.0
Total		500 mL		

	Dose Level 18 mg/kg			
	Volume 500 mL, body weight 80 kg, 2.9 mg/mL			
Time - min	mL/hr	mL/30min	mg/30min	mg/min
0-30	100	50	144	4.8
31-60	200	100	288	9.6
61-90	300	150	432	14.4
91-120	400	200	576	19.2
Total		500 mL		

Abbreviations (in alphabetical order): hr, hour; min, minute

For all subsequent infusions, the infusion rate will be according to the trial site standard practices for iv administration of mAbs and no faster than the highest safest rate administered during Cycle 1.

7.1.4.6 Patient Monitoring During and After Infusion of Sym004

Patients will be treated on an outpatient basis.

Sym004 infusions should be administered under the close supervision of an experienced physician in an environment where full resuscitation facilities are immediately available. At the end of each infusion, the iv line must remain in place for at least 1 hour to allow administration of iv drugs, if necessary.

Patients will be 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.

7.1.4.7 Infusion-Related Reactions to Sym004

An Infusion-Related Reaction (IRR) is defined as an AE occurring during the Sym004 infusion and up to 2 hours (or longer, if considered by the Investigator to be an IRR) after the EOI, which is assessed by the Investigator to be related to the infusion of Sym004.

7.1.4.8 Handling of Infusion-Related Reactions

If an IRR occurs, it should be classified according to CTCAE and the management guidelines shown in Table 5 should be followed.

Table 5 Infusion-Related Reactions Management Guidelines

CTCAE Grade	Management/Treatment
<p>Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated</p>	<ul style="list-style-type: none"> Continue infusion Monitor closely
<p>Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 h</p>	<ul style="list-style-type: none"> Interrupt Sym004 infusion for a minimum of 30 minutes. Administer symptomatic treatment (e.g. antihistamines, NSAIDs, etc.) Use supportive treatment (e.g. bronchodilator, oxygen, etc.), if necessary When symptoms have resolved and the patient is clinically stable, restart infusion at half the previous rate (when the IRR occurred) and monitor vital signs closely during the entire infusion If the vital signs remain stable and symptoms do not recur, the infusion rate can be increased at the discretion of the Investigator Monitor closely If symptoms reoccur, stop the infusion, institute remedial therapy, monitor closely and evaluate whether the patient can continue the trial
<p>Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae</p>	<ul style="list-style-type: none"> Discontinue Sym004 infusion Administer symptomatic and supportive treatment (e.g. bronchodilator, antihistamine, glucocorticoid, iv fluid, oxygen, etc.) as needed Either withdraw the patient from treatment or continue subsequent treatments at a reduced dose Premedication should be reinstated if previously discontinued
<p>Grade 4 Life-threatening consequences; urgent intervention indicated</p>	<ul style="list-style-type: none"> Stop Sym004 infusion Administer necessary life-support measures as needed Withdraw the patient from treatment

Abbreviations (in alphabetical order): CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03; h, hours; IRR, Infusion-related Reaction; iv, intravenous; NSAID, nonsteroidal anti-inflammatory drug

7.1.5 Dose-Adjustments and Delays of Sym004

The dose of Sym004 in mg/kg, assigned to the individual patient, will be confirmed by the Sponsor or designee prior to C1/D1.

Based on the body weight of the patient, the site will calculate the nominal dose of Sym004 to be administered in mg.

Weight changes ($\geq \pm 10\%$) for a patient during trial will require recalculation of the dose ([Section 7.1.5.1](#)).

Furthermore, dose delays of Sym004 and intra-patient dose-reduction(s) may also be required upon occurrence of Grade 3 anti-EGFR-associated skin toxicity ([Section 7.1.5.2](#)) and other safety events ([Section 7.1.5.3](#)). Dose adjustments should be discussed with the Sponsor or designee prior to implementation.

If Sym004 administration is delayed, subsequent dosing will be resumed in combination with a scheduled FOLFIRI administration.

7.1.5.1 Sym004 Dose-Adjustments for Body Weight

Sym004 is dosed in mg/kg and the dose to be administered will be calculated based on the actual body weight of the patient. The dose calculated may be used for subsequent infusions, unless body weight changes $\geq \pm 10\%$ from screening, in which case the dose must be adjusted according to the change in body weight. Adjustment may be made in the event of lesser incremental changes in weight at the site's discretion.

7.1.5.2 Sym004 Dose-Modifications for Skin Toxicity

The infusion of Sym004 must be paused in the event of a Grade 3 skin toxicity, by delaying the dose of Sym004 resulting in a period of approximately 28 days between 2 Sym004 administrations.

If Sym004 is paused, all per protocol scheduled assessments must be done and FOLFIRI will be administered according to the planned schedule and [Section 7.2.1](#).

Sym004 dosing will subsequently be resumed in combination with a scheduled FOLFIRI administration and according to specific instructions on dose-delays and dose-reductions provided in [Table 6](#).

Table 6 Sym004 Dose-Reduction for Grade 3 Skin Toxicity

Skin Toxicity Grade 3	Sym004 Immediate Action	Outcome Improvement	Sym004
First occurrence	Delay dose	Yes, Grade 2	Reduce by 3 mg/kg
		Yes, Grade ≤1	Continue at same dose
		No	Discontinue
Second occurrence	Delay dose	Yes, Grade 2	Doses at 9 mg/kg or above: Reduce by 3 mg/kg Dose at 6 mg/kg: Reduce by 1.5 mg/kg
		Yes, Grade ≤1	Continue at same dose
		No	Discontinue
Subsequent occurrences	Delay dose	Yes, Grade 2	Doses at 9 mg/kg or above: Reduce by 3 mg/kg Dose at 6 mg/kg: Reduce by 1.5 mg/kg Dose at 4.5 mg/kg: Discontinue
		Yes, Grade ≤1	Continue at same dose
		No	Discontinue

In case of a Grade 2 skin toxicity, which is locally debilitating for the patient, the guidelines outlined in [Table 6](#) above may be followed at the Investigator’s discretion.

In the occurrence of fissures unresponsive to intensive therapeutic treatment as specified in [Table 15](#), the dose of Sym004 should be delayed or reduced. The need for > 2 week dose delays or dose-reduction should be discussed with the Sponsor or designee if adequate improvement is not seen after the initial delay.

7.1.5.3 Sym004 Dose-Modifications for Events other than Grade 3 Skin Toxicity

In the occurrence of hypomagnesemia Grade 4, refractory to iv magnesium-replacement therapy as specified in [Section 7.2.5](#), dosing of Sym004 may be delayed or reduced. The need for > 2 week dose delays or dose-reduction should be discussed with the Sponsor or designee if adequate improvement is not seen after the initial delay.

Sym004 will not be delayed for FOLFIRI-related toxicities. FOLFIRI dosing will be resumed in combination with the next scheduled Sym004 administration once related toxicities have resolved.

7.2 Other Drugs to be used in the Trial

7.2.1 FOLFIRI

The FOLFIRI regimen consists of:

- Irinotecan 180 mg/m² iv, infused over 60-90 minutes, concurrently with
- Folinic Acid (FA) 400 mg/m² iv, infused over 120 minutes, followed by

- 5-Fluorouracil (5-FU) 400 mg/m² iv bolus, then 2400 mg/m² 5-FU infused over 46 hours

This regimen is typically repeated every 2 weeks. For the purposes of this trial, FOLFIRI will be administered on the same schedule as Sym004 i.e. every second week (Day 1 and Day 15 of each 28 day cycle, ± 2 days).

7.2.1.1 FOLFIRI Delays and Dose-Reduction

On the planned day of treatment, FOLFIRI may be administered only if the following treatment criteria are met:

- ANC $\geq 1.5 \times 10^9/L$ (1500/mm³)
- Platelet count $\geq 100 \times 10^9/L$ (100,000/mm³)
- FOLFIRI-related gastrointestinal toxicity is \leq Grade 1

If any of the above criteria are not met, all components of FOLFIRI dosing will be delayed. If FOLFIRI administration is delayed subsequent dosing will be resumed in combination with a scheduled Sym004 administration.

In the event of toxicities other than those listed above, dose-adjustments of the components of FOLFIRI should be made independently, based on the toxicity observed.

Table 7 presents the recommended dose-reductions for each of the components of FOLFIRI for which dose-modifications will be allowed. If a dose-reduction exceeding that represented by Dose Level -3 is required for any agent, that agent should be discontinued.

Table 7 FOLFIRI Dose-Reductions

FOLFIRI Component	Dose Level			
	Initial Dose	-1	-2	-3
Irinotecan	180 mg/m ²	150 mg/m ²	120 mg/m ²	100 mg/m ²
5-FU Bolus	400 mg/m ²	200 mg/m ²	0 mg/m ²	0 mg/m ²
5-FU Infusion	2400 mg/m ² over 46-48 hours	2000 mg/m ² over 46-48 hours	1600 mg/m ² over 46-48 hours	1200 mg/m ² over 46-48 hours

Abbreviations: 5-FU, Fluorouracil

FOLFIRI guidelines for dose modifications and delays are provided (refer to Appendix 2). If other symptoms not discussed in Appendix 2 occur, the Sponsor or designee should be consulted.

General dosing considerations are as follows:

- If 5-FU/FA administration is delayed, irinotecan treatment must also be postponed, although Sym004 administration may continue without postponement

- If irinotecan administration is delayed, 5-FU/FA treatment must also be postponed, although Sym004 administration may continue without postponement
- No dose-reductions will be implemented for FA; however, FA will always be withheld when 5-FU is held
- In general, if a dose is reduced because of toxicity, it should not be re-escalated to the starting level. However, patients who require dose-reductions during a cycle for Grade 2 toxicity may, at the investigator's discretion, begin the following cycle at 1 dose level higher than the final dose level during that cycle
- If FOLFIRI is withheld because of toxicity for more than 1 cycle (approximately 28 days), FOLFIRI will be discontinued; Sym004 may be continued if the toxicity resulting in FOLFIRI discontinuation is not considered by the investigator to be related to Sym004.

For hypersensitivity reactions due to infusion of irinotecan or 5-FU, treatment should be administered as per institutional guidelines and/or at the discretion of the Investigator.

7.2.2 Order of Sym004 and FOLFIRI Administration

Sym004 and FOLFIRI administration will be initiated on Day 1 and Day 15 (\pm 2 days) of each 28 day cycle. The Sym004 infusion will be delivered first. The FOLFIRI regimen administration will commence no sooner than 1 hour following completion of Sym004 administration.

7.2.3 Prophylactic Treatment

7.2.3.1 Prophylactic Treatment for Infusion Reactions

There is an inherent risk for IRRs with the administration of mAbs. A premedication schedule will therefore be implemented for all patients treated.

Prior to the first 2 infusions of Sym004 (i.e. during Cycle 1) all patients will receive:

- Glucocorticoid therapy equivalent to 80-100 mg iv methylprednisolone, approx. 0.5 to 2 hours prior to the start of Sym004 infusion
- Antihistamine (H1 antagonist) equivalent to 25-50 mg iv diphenhydramine, approx. 0.5 hours prior to the start of Sym004 infusion

For infusion following the completion of Cycle 1, pre-medication is at the Investigators discretion. Premedication should be reinstated in the event of Grade \geq 3 IRR.

7.2.3.2 Prophylactic Treatment for Gastrointestinal Toxicities

To minimize the risk of gastrointestinal side-effects related to FOLFIRI and/or Sym004, all patients will receive:

- Prophylaxis for nausea and vomiting according to institutional standards

- Mandatory prophylaxis for diarrhea as shown in [Table 8](#). Loperamide therapy may be continued beyond end of Cycle 1 (C1) at the Investigator’s discretion.

Table 8 Mandatory Prophylaxis for Diarrhea

Treatment	Dose	Start	Stop
Loperamide	4 mg po prior to start of FOLFIRI 4 mg tid	C1/D1	C1/D2
	4 mg tid	C1/D2	C1/D3
	2 or 4 mg tid or qid as required	C1/D4	End of C1

Abbreviations: C1/D1, Day 1 of Cycle 1; po, per os; tid, three times per day; qid, four times per day

- 1) Loperamide may be continued beyond end of Cycle 1 (C1) at the Investigator’s discretion
- 2) If the patient is experiencing \geq G2 diarrhea continuation of loperamide therapy at 4 mg on an up to qid schedule is permissible.
- 3) These recommendations do not supersede the recommendations for treatment or prophylaxis of early diarrhea due to irinotecan nor do they alter the recommendations for dose reduction of 5-FU or irinotecan as specified in [Appendix 2](#).

7.2.3.3 Prophylactic Treatment for Skin Toxicity

All patients will receive mandatory prophylactic treatment for skin toxicities and may be continued beyond end of Cycle 2 (C2) at the Investigator’s discretion as described in [Table 9](#).

Table 9 Mandatory Prophylaxis for Skin Toxicities

Treatment	Dose	Start	Stop	Alternatives
SYSTEMIC THERAPY¹				
Minocycline or Doxycycline	1 × 100 mg/day 2 × 100 mg/day	C1/D1	End of C2 ²	In case of intolerance: <ul style="list-style-type: none"> • First generation cephalosporins • Amoxicillin • Erythromycin • Limecycline
TOPICAL THERAPY				
Low potency steroid creams such as <ul style="list-style-type: none"> • Alclometasone 0.05% • Desonide 0.05 % • Fluocinolone 0.01% 	2 × daily on face and chest	C1/D1	End of C2	
Moisturizer (creams or ointments)	3 × daily to hands, and after hand washing using fragrance-free soaps 2 × daily to rest the body	C1/D1	Continue	

Abbreviations: C1/D1, Day 1 of Cycle 1; C2, Cycle 2

- 1) If infection is suspected (yellow crusts, purulent discharge, painful skin/nares) obtain culture and change to oral antibiotic based on sensitivities
- 2) May be continued beyond end of Cycle 2 (C2) at the Investigator’s discretion

7.2.4 Treatment of Skin Toxicity

Recommendations for management of Grade 1 to 3 Sym004 induced skin toxicities, i.e. rash, xerosis, paronychia, pruritus, photosensitivity and fissures, are summarized in [Table 10](#) to [Table 15](#) below.

In the event that a patient experiences any Grade 4 skin toxicity, the patient must be withdrawn from Sym004 treatment.

It is strongly recommended that a dermatologist is consulted in the event of Grade 3 or 4 skin toxicity.

Table 10 Treatment of Rash

CTCAE Grade	Action with Sym004	Treatment
<p>Grade 1 Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness</p>	<p>Continue at the same dose</p>	<p>Topical: Face and Chest</p> <ul style="list-style-type: none"> • Steroid creams of low potency (alclometasone 0.05%, desonide 0.05% or fluocinolone 0.01%), 2 × daily, <p>Rest-of-body</p> <ul style="list-style-type: none"> • Moisturizers, 2 × daily, rest of body <p>Systemic¹:</p> <ul style="list-style-type: none"> • Minocycline 100 mg/day or doxycycline 200 mg/day at least 4 weeks
<p>Grade 2 Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limited instrumental ADL</p>	<p>Continue at the same dose</p> <p>If locally debilitating for the patient, consider to follow guidelines of dose-delay and dose-reduction as outlined in Table 6</p>	<p>Topical:</p> <ul style="list-style-type: none"> • See Grade 1 <p>Systemic¹:</p> <ul style="list-style-type: none"> • Minocycline 100 mg/day or doxycycline 200 mg/day for at least 4 weeks • 1 week course of oral steroid: Methylprednisolone 4 mg tablets: Day 1: 2-1-1-2, Day 2: 1-1-1-2, Day 3: 1-1-1-1, Day 4: 1-1-1, Day 5 1-0-1, Day 6: 1
<p>Grade 3 Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated</p>	<p>Delay dose of Sym004, continue skin treatment and re-asses. Refer to Table 6 for further guidelines on dose-reduction</p>	<p>Topical:</p> <ul style="list-style-type: none"> • See Grade 1 <p>Systemic¹:</p> <ul style="list-style-type: none"> • See Grade 2

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03

- 1) Alternatives in case of intolerance: First generation cephalosporins, amoxicillin, erythromycin or limecycline. If infection is suspected (yellow crusts, purulent discharge, painful skin/nares): Obtain culture and change to oral antibiotic based on sensitivities

Table 11 Treatment of Xerosis

CTCAE Grade	Action with Sym004	Treatment
<p>Grade 1 <10% BSA and no associated erythema or pruritus</p>	<p>Continue at the same dose</p>	<p>Topical: Face</p> <ul style="list-style-type: none"> Moisturizing cream or ointment¹, 2 × daily <p><u>And</u></p> <p>Body</p> <ul style="list-style-type: none"> Ammonium lactate 6-12% cream, 2 × daily
<p>Grade 2 10-30% BSA associated with erythema or pruritus; limited instrumental ADL</p>	<p>Continue at the same dose</p> <p>If locally debilitating for the patient, consider to follow guidelines of dose-delay and dose-reduction as outlined in Table 6</p>	<p>Topical: Face</p> <ul style="list-style-type: none"> Moisturizing cream or ointment¹, 2 × daily <p><u>And</u></p> <p>Body</p> <ul style="list-style-type: none"> Ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream, 2 x daily
<p>Grade 3 >30% BSA associated with pruritus; limited self-care ADL</p>	<p>Delay dose of Sym004, continue skin treatment and re-asses. Refer to Table 6 for further guidelines on dose-reduction</p>	<p>Topical: Face</p> <ul style="list-style-type: none"> Moisturizing cream or ointment¹, 2 × daily <p><u>And</u></p> <p>Body</p> <ul style="list-style-type: none"> Ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream, 2 × daily; <u>and</u> Eczematous areas: Topical steroid (e.g. triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, fluticasone propionate 0.05%), 2 × daily

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03

- 1) If prescription is not available, recommendation by pharmacist/dermatologist is acceptable

Table 12 Treatment of Paronychia

CTCAE Grade	Action with Sym004	Treatment
<p>Grade 1 Nail fold edema or erythema; disruption of the cuticle</p>	<p>Continue at the same dose</p>	<p>Topical:</p> <ul style="list-style-type: none"> Antibiotics (e.g. clindamycin 1%, erythromycin 1%) <u>and</u> Vinegar soaks (i.e. soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day <p><u>And</u> Systemic:</p> <ul style="list-style-type: none"> Bacterial culture, oral antibiotic if infection confirmed
<p>Grade 2 Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL</p>	<p>Continue at the same dose</p> <p>If locally debilitating for the patient, consider to follow guidelines of dose-delay and dose-reduction as outlined in Table 6</p>	<p>Same as for Grade 1</p> <p><u>And</u> Topical:</p> <ul style="list-style-type: none"> Silver nitrate application weekly (needs consultation with dermatologist or surgeon)
<p>Grade 3 Surgical intervention or iv antibiotics indicated; limiting self-care ADL</p>	<p>Delay dose of Sym004, continue skin treatment and re-asses. Refer to Table 6 for further guidelines on dose-reduction</p>	<p>Same as for Grade 1</p> <p><u>And</u></p> <ul style="list-style-type: none"> Silver nitrate application weekly (needs consultation with dermatologist or surgeon) <p><u>And</u></p> <ul style="list-style-type: none"> Consider nail avulsion (needs consultation with dermatologist or surgeon)

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03; iv, intravenous

Table 13 Treatment of Pruritus

CTCAE Grade	Action with Sym004	Treatment
<p>Grade 1 Mild or localized; topical intervention indicated</p>	<p>Continue at the same dose</p>	<p>Topical:</p> <ul style="list-style-type: none"> • Steroid (e.g. triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, Fluticasone propionate 0.05%), 2 × daily <p style="text-align: center;"><u>or</u></p> <ul style="list-style-type: none"> • Anti-pruritics (e.g. pramoxine 1%, doxepin 5% cream), 2 × daily
<p>Grade 2 Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</p>	<p>Continue at the same dose</p> <p>If locally debilitating for the patient, consider to follow guidelines of dose-delay and dose-reduction as outlined in Table 6</p>	<p>Same as for Grade 1</p> <p>And</p> <p>Systemic:</p> <ul style="list-style-type: none"> • Oral antihistamines (diphenhydramine 25-50 mg; hydroxyzine 25 mg; fexofenadine 60 mg, 3 × daily
<p>Grade 3 Intense or widespread; constant; limiting self-care, ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</p>	<p>Delay dose of Sym004, continue skin treatment and re-asses. Refer to Table 6 for further guidelines on dose-reduction</p>	<p>Same as for Grade 2</p>

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03

Table 14 Treatment of Photosensitivity

CTCAE Grade	Action with Sym004	Treatment
<p>Grade 1 Painless erythema and erythema covering <10% BSA</p>	<p>Continue at the same dose</p>	<p>Topical:</p> <ul style="list-style-type: none"> Broad spectrum sunscreen with an SPF of at least 15; need to be applied every 2 hours or more frequently if swimming or perspiring <p>And</p> <p>Systemic:</p> <ul style="list-style-type: none"> Bacterial culture, oral antibiotic if infection confirmed
<p>Grade 2 Tender erythema covering 10-30% BSA</p>	<p>Continue at the same dose</p> <p>If locally debilitating for the patient, consider to follow guidelines of dose-delay and dose-reduction as outlined in Table 6</p>	<p>Same as for Grade 1</p> <p>And</p> <p>Topical:</p> <ul style="list-style-type: none"> Corticosteroids (e.g. triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05% cream, fluticasone propionate 0.05%), 2 × daily
<p>Grade 3 Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g. narcotics or NSAIDs)</p>	<p>Delay dose of Sym004, continue skin treatment and re-asses. Refer to Table 6 for further guidelines on dose-reduction</p>	<p>Same as Grade 2</p>

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03; NSAID, nonsteroidal anti-inflammatory drugs; SPF, sun protection factor

Prophylaxis of fissures includes careful use of moisturizing creams and/or ointments 3 times a day and after handwashing, using only fragrance-free soaps. Should fissures begin to form, a stepwise approach outlined in [Table 15](#) should be followed.

Table 15 Treatment of Fissures

Treatment Step	Action with Sym004	Treatment
Step 1 Initiated at first occurrence	No action	Topical: <ul style="list-style-type: none"> Thick moisturizers of zink oxide (13-40%) cream Liquid glues of cyanoacrylate to seal cracks
Step 2 If no improvement after 2 weeks from initiation of Step 1	No action	Topical: <ul style="list-style-type: none"> Thick moisturizers of zink oxide (13-40%) cream under occlusion at night Salicylic acid 6% cream <u>or</u> ammonium lactate/lactic acid 12%
Step 3 If no improvement after 2 weeks from initiation of Step 2	Delay dose of Sym004 and re-assess. Discuss need for dose-reduction and/or further dose omissions with Sponsor or designee	Continue local treatment as described in Step 2

7.2.5 Treatment of Hypomagnesemia

In the event that a patient experiences Grade 3 or 4 hypomagnesemia, treatment with iv magnesium sulphate 6-10 g or equivalent should be given at least twice a week until magnesium levels are \leq Grade 1.

A 12-lead ECG should be performed prior to administration of the next dose of Sym004 for monitoring of QT prolongation which may result in Torsade de Pointes (TdP) arrhythmias. In the event of TdP arrhythmia or any other life-threatening cardiac arrhythmia, the patient should be withdrawn from treatment with Sym004.

7.3 Blinding

Not applicable as this is an open-label trial.

7.4 Drug Accountability and Compliance Check

The Investigator is responsible for ensuring accountability for the IMP, including maintenance of IMP accountability records.

IMP accountability records will include a full inventory of the IMP including:

- Confirmation of IMP delivery to the trial site
- Record of each dose dispensed
- The return of unused IMP to the Sponsor or designee

Records will specify dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The Investigator, or designee, should maintain records that adequately document:

- That the patients were provided the doses specified by the CTP, and
- That all IMP provided by the Sponsor was fully reconciled

7.5 Concomitant Medication/Therapy

7.5.1 Allowed Concomitant Medication/Therapy and Procedures during the Trial

Patients may receive their current concomitant medication and any medication considered necessary for the welfare of the patient during trial, except if listed in [Section 7.5.2](#).

Furthermore, the following medications and procedures are permitted during the trial:

- Premedication with standard therapies prior to Sym004 administration to reduce the risk of IRRs
- Prophylaxis and treatment of Sym004 and FOLFIRI related toxicities
- Prophylactic use of blood products and growth factors after Cycle 1. Interventional/therapeutic use is allowed at any time
- Radiotherapy for pain control against non-target lesions, as long as it does not influence bone marrow function

7.5.2 Prohibited Concomitant Medication/Therapy and Procedures during the Trial

The following medications and procedures are not allowed from C1/D1, or as specified in the inclusion/exclusion criteria, until the EOT Visit:

- Anti-cancer treatment, including cytotoxic or cytostatic agents, hormonal therapy (except as physiologic hormone replacement), other anti-EGFR antibodies or anti-EGFR small molecule inhibitors
- Radiotherapy against target lesion(s)
- Systemic immunosuppressive or systemic hormonal therapy with the exception of the following allowed therapies:

- a. Hormonal therapy (e.g., Megace) for appetite stimulation
 - b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
 - c. Oral replacement glucocorticoid therapy for adrenal insufficiency
 - d. Low-dose maintenance steroid/hormonal therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation)
 - e. Hormonal contraceptive therapy
- Prophylactic use of hematopoietic growth factors during Cycle 1
 - Major surgery that would preclude the patient from complying with the requirements of the protocol

If any one of the above listed medications/procedures becomes necessary during the trial, the patient must be withdrawn from Sym004 and FOLFIRI and the EOT Visit should be performed. The 1M FUP Visit should then be conducted, no less than 1 month (28 +7 days) after withdrawal from trial treatments.

7.6 Medical Care of Patients after End of Trial Participation

After completing participation in this trial, patients will be offered standard of care treatment in accordance with generally accepted medical practice and depending on the patient's individual medical need.

8 TRIAL ASSESSMENTS

8.1 Baseline Characteristics / Eligibility Assessments

8.1.1 Signing of Informed Consent

Prior to any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.

- Screening

NOTE: In the event a tumor biopsy is required for eligibility, informed consent may be obtained outside the 14-day screening period prior to C1/D1

8.1.2 Demographics

To include date of birth, sex, race and ethnicity.

- Screening

8.1.3 Medical History

To include details of prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

- Screening
- C1/D1 (prior to dosing)

8.1.4 Tumor Characteristics and Extent of Disease

To include details of diagnosis and date of initial diagnosis, Tumor Node Metastasis (TNM) staging at time of initial diagnosis, tumor histology, current location of metastases, date of most recent disease progression and mutation status.

- Screening

8.1.5 Prior Cancer Treatments

To include details of prior surgical procedures for the primary diagnosis, as well as prior radiotherapy, chemotherapy and/or biological targeted therapy, investigational treatments and/or procedures. Include dates of treatments, numbers of cycles, and best response to such treatments.

- Screening
- C1/D1 (prior to dosing)

8.2 Safety Assessments

To be performed within 14 days of C1/D1 (first dose of Sym004/FOLFIRI), unless otherwise specified.

8.2.1 Medication Survey

To include details of all medications and/or treatments taken other than Sym004 or FOLFIRI. Include generic name or brand name, indication for use, dose and frequency, route of administration, start and stop dates or if ongoing at 1M FUP Visit

- Starting from the date of Screening
- Until the date of the 1M FUP

8.2.2 Adverse Event Survey

For details about (S)AEs and (S)AE reporting, refer to [Section 9](#).

- Starting from signing the informed consent until the date of the 1M FUP

NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial

8.2.3 Dose-Limiting Toxicities Evaluation (Dose-Escalation Only)

For details about AEs meeting DLT criteria, refer to [Section 9.5](#).

- Starting from the first dose of trial drug (C1/D1)
- Reported during Cycle 1 with final assessment 14 days (± 2) after the second dose of Cycle 1 or prior to dosing on the scheduled Day 1 of Cycle 2 (C2/D1)

8.2.4 Vital Signs and Body Weight

To include temperature, heart rate, blood pressure, and body weight.

- Screening
- Day 1 and 15 of each cycle (prior to dosing)
- EOT
- 1 M FUP
- As clinically indicated

8.2.5 Performance Status

To be assessed by ECOG PS score.

- Screening

- Day 1 of each cycle (prior to dosing)
- EOT
- 1 M FUP
- As clinically indicated

8.2.6 Physical Examination

To include evaluation of: General appearance, head, ears, eyes, nose, throat, neck/thyroid, chest, cardiovascular system, abdomen, musculoskeletal system, pulses, lymph nodes, neurologic status and mental status. At Screening, include height (without shoes, rounded to nearest centimeter).

- Screening
- Day 1 of each cycle (prior dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.7 Dermatological Assessment

To be performed by a physician or qualified designee; complete skin examination

- Screening
- Day 1 and 15 of each cycle (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.8 Electrocardiogram

To include standard 12-lead ECG. The Investigator, or qualified designee, should document the evaluation of the ECG, including specification of any abnormality as clinically significant or not clinically significant.

- Screening
- EOT
- In the event of \geq Grade 3 hypomagnesemia an ECG is to be scheduled as soon as possible

- In the event of QT prolongation an ECG is to be performed prior to the next dose of Sym004
- As otherwise clinically indicated
- In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.

8.2.9 Laboratory Assessments and Pregnancy Test

All routine laboratory analyses will be performed at a laboratory facility local to the trial site. Results should be available to confirm eligibility and prior to each dosing of Sym004 and FOLFIRI.

Sponsor or designee must be provided with a list of trial site laboratory normal ranges for all required parameters prior to screening of the first patient at the site. Likewise, any change in laboratory normal ranges during the trial should be forwarded to the Sponsor or designee promptly during the trial.

Blood samples will be taken at all visits and analyzed for the following parameters as per [Table 16](#) and as clinically indicated:

Table 16 Schedule of Safety Blood and Urine Samples

Sample Analysis	Screening	Cycle 1				Cycles Thereafter		EOT	1M FUP
		D1	D8	D15	D22	D1	D15		
Day within Cycle									
Hematology Panel	X	X	X	X	X	X	X	X	X
Biochemistry Panel	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X		X		X	X
Pregnancy Test	X							X	

Abbreviations (in alphabetical order): D, day; EOT, End of Treatment Visit; 1M FUP, One Month Follow-up Visit

8.2.9.1 Hematology Panel

To include complete blood count with differential, ANC, and platelet count.

- Screening
- Cycle 1
 - a. Day 1 and 15 (prior to dosing)
 - b. Day 8 and 22
- Each cycle thereafter

- a. Day 1 and 15 (prior to dosing)
 - EOT
 - 1M FUP
 - As clinically indicated

In the event of hematologic toxicity, the evaluation frequency should be increased to include additional evaluations between scheduled assessments, as clinically indicated.

8.2.9.2 Biochemistry Panel

To include, if applicable, sodium, potassium, chloride, bicarbonate or carbon dioxide, Blood Urea Nitrogen (BUN), creatinine, glucose, bilirubin [total and direct], AST, ALT, Alkaline Phosphatase (ALP), calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, and Creatine Kinase (CK). Clinically significant electrolyte abnormalities should be corrected prior to dosing.

- Screening
- Cycle 1
 - a. Day 1 and 15 (prior to dosing)
 - b. Day 8 and 22
- Each cycle thereafter
 - a. Day 1 and 15 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

In the event of significant biochemistry analyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. In the event of CK abnormalities, isoenzyme analysis should be performed.

8.2.9.3 Coagulation Panel

To include PT, PTT and INR.

- Screening
- Cycle 1
 - a. Day 1 and 15 (prior to dosing)
 - b. Day 8 and 22

- Each cycle thereafter
 - a. Day 1 and 15 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.9.4 Urinalysis

Multi-parameter chemical test strips are acceptable and should include assessment of: Specific gravity, pH, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

- Screening
- Cycle 1
 - a. Day 1 and 15 (prior to dosing)
- Day 1 of each cycle thereafter (prior dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.9.5 Pregnancy Test

Serum human Chorionic Gonadotropin (β -hCG) at screening, urine β -hCG thereafter, in women of childbearing potential.

- Screening
- EOT
- As clinically indicated

Women are considered of childbearing potential unless they have been hysterectomized, have undergone tubal ligation or have been postmenopausal for at least one year.

8.3 Disease Assessments

8.3.1 Tumor Marker Evaluation

To include Carcinoembryonic Antigen (CEA). Will be performed at a laboratory facility local to the trial site.

- Screening
- End of Cycle 2 and end of every second cycle thereafter, i.e. Cycle 4, 6, 8 etc.

NOTE: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle

- At least 28 days following an OR (PR, CR)
- EOT (if > 3 weeks since previous evaluation)
- 1M FUP (if PD was not documented before or at EOT)

8.3.2 Disease Status Evaluation using CT or MRI

The anti-tumor activity of Sym004 in combination with FOLFIRI will be assessed by the Investigator, or qualified designee, according to RECIST v1.1. Refer to [Appendix 1](#).

Patients will undergo imaging of the thorax, abdomen, and pelvis by CT or MRI as indicated, based on tumor type and prior areas of documented disease. The use of CT or MRI must be consistent per patient throughout the trial. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

- Screening

NOTE: A CT/MRI performed within 28 days prior to Day 1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the protocol requirements

- End of Cycle 2 and end of every second cycle thereafter, i.e. Cycle 4, 6, 8 etc.

NOTE: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle

- Suspected PD (as soon as possible)
- At least 28 days following an OR (PR, CR)
- EOT (if > 3 weeks since previous CT/MRI)
- At 1M FUP (if PD was not documented before or at EOT)

If disease progression is documented at any time, no further disease assessments will be required. Patients with documented PD will be discontinued from further treatment with Sym004/FOLFIRI so that alternative management of their malignancy may be considered.

To be assigned a status of confirmed PR or CR, changes in disease status must be confirmed by repeat studies performed no less than 28 days (4 weeks) after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimal interval in general no less than 6-8 weeks.

Imaging data will be stored by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer.

For all imaging time points, the following will be recorded as per RECIST v1.1: Target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target

lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal); final response assessment at each visit (PD, SD, PR, CR or Not Evaluable [NE])

8.4 Pharmacokinetic Assessments (Dose-Escalation Only) [Omitted as of Amendment 3]

PK samples will be taken according to the schedules shown in Table 17 for patients in dose-escalation only. Per sampling, approximately 5 mL of blood will be obtained from patients to measure Sym004 concentration in serum.

Analysis of PK will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage and shipment will be provided to the trial sites.

In the event that a collected serum sample is inadequate for PK analysis, the analysis of PK can be done using an ADA serum sample from the same time point, if available.

Table 17 Schedule of Pharmacokinetic Assessments

		Cycle 1		Cycle 2		Cycles Thereafter	EOT	1M FUP
		D1	D15	D1	D15	D1		
Sampling Time	Window							
SOI	- 4 h	X	X	X ¹	X ^{1,2}	X ¹		
EOI	+ 10 min	X	X	X	X	X		
EOI + 1 h	+/- 15 min	X			X			
EOI + 2 h	+/- 30 min	X			X			
EOI + 4 h	+/- 30 min	X			X			
EOI + 24 h	+/- 6 h	X			X			
EOI + 48 h	+/- 12 h	X			X			
During Visit	NA						X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion, EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; 1M FUP, One Month Follow-up Visit; SOI, Start of Infusion

- 1) If Sym004 is paused, only one PK sample should be taken during the visit
- 2) If Sym004 is paused, the scheduled extended PK profile samples (i.e. additional timepoints EOI + 1, 2, 4, 24 and 48 hours) should be postponed until the 4th administration of Sym004 takes place

8.5 Anti-Drug Antibody Testing (Omitted as of Amendment 3)

To assess formation of ADA. All samples must be taken prior to the Sym004 infusion of that visit. Per sampling, approximately 5 mL of blood will be obtained for preparation of serum. Analysis of ADA and residual serum levels of Sym004 will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage and shipment will be provided to the trial sites. In the event that a collected serum sample is inadequate for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same time point, if available.

- C1/D1

- Prior to every second cycle thereafter, i.e. Cycle 3, 5, 7 etc.
- EOT
- 1M FUP

8.6 Biomarker Tumor, Blood and Urine Sample (Omitted as of Amendment 3)

To be performed only after eligibility has been confirmed.

8.6.1 Archival Tumor Sample Collection (Omitted as of Amendment 3)

If available, archived formalin-fixed paraffin-embedded (FFPE) tumor tissue sample from a prior surgical procedure or biopsy to be submitted to a central laboratory for evaluation of RAS mutations; tissue block or cut/unstained slides are acceptable. This sample could be taken at any time from the time of diagnosis to the time of enrollment into this trial. All tumor tissue samples should be reviewed by a pathologist to confirm the presence of tumor cells before the tissue sample is sent to the central laboratory for analysis. Unused portions of paraffin blocks will be returned to the referring institution if requested. Procedures for handling and shipment will be provided.

- Screening

8.6.2 Fresh Tumor Biopsy Collection (Omitted as of Amendment 3)

To be performed only if archival FFPE tumor samples (blocks or slides) are not available for submission and only after eligibility has been confirmed.

The patient will have a tumor core biopsy of a locally recurrent or metastatic lesion. This procedure will take place after eligibility has been confirmed and prior to first Sym004 administration. The tumor biopsy must be performed with minimal morbidity to the patient by a percutaneous core biopsy needle either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy.

Biopsy specimens will be obtained using standard sterile surgical techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. All tumor tissue samples should be reviewed by a pathologist to confirm the presence of tumor cells before the tissue sample is sent to the central laboratory for analysis.

- Screening (after confirmation of eligibility and only if archival tumor tissue sample is not available for central analysis)

Biomarker testing from collected tumor biopsies (archival FFPE or fresh tumor biopsy) will, if amount of tissue allows, in addition to RAS and EGFR, include biomarkers connected to EGFR signaling or escape mechanisms observed after EGFR treatment.

8.6.3 Blood and Urine Sample Collection (Omitted as of Amendment 3)

The purpose of the pharmacodynamics biomarker assessments is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Sym004, and that may change with the possible development of acquired resistance to Sym004. Potential biomarkers of interest includes genes, gene transcripts and proteins of the Receptor Tyrosine Kinases (RTKs) and molecules of the EGFR signaling pathway.

Analysis of all samples taken for pharmacodynamics assessments will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage and shipment will be provided to the trial sites.

Patients will have blood samples taken of approximately 20 mL, for preparation of plasma, and a urine sample of approximately 100 mL.

- Screening
- End of Cycle 2 (prior to dosing or upon PD, whichever occurs first)

NOTE: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle

- EOT

8.7 Handling of Biological Samples

All biological samples to be analyzed locally will be collected and handled according to institutional practices.

All biological samples to be analyzed centrally will be collected and handled according to a detailed laboratory manual.

Retention time for biologic specimens will be specified in the laboratory manual.

8.8 Follow-up Assessments

Assessments at the 1M FUP Visit include disease status and subsequent cancer therapy.

8.9 Appropriateness of Measurements

Standardized methods for assessments of efficacy and safety variables will be used.

9 ADVERSE EVENTS

9.1 Definitions of Adverse Events

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Please Note: Progression of disease will not be captured as an AE/SAE unless the nature of the PD is different than expected (i.e. other diagnoses and/or signs/symptoms that are not typical of PD). Events associated with the actual PD will also be captured, as determined by the investigator. Additionally, AE occurring simultaneously with PD, but which may not be related to the actual PD, will also be captured.

Causality for the above-mentioned AE will be assessed appropriately as; Related to Study Drug, Not Related to Study Drug or Related to Disease Progression. In addition, any AE, regardless of causality, that also meets seriousness criteria, will be reported on an SAE Form

Events not to be considered as Adverse Events

A pre-existing condition (i.e., a disorder that is present before the AE recording period starts and is noted on the medical history/physical examination form) should not be recorded as an AE unless the condition worsens or episodes increase in frequency during the AE recording period.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be recorded as AEs. A medical condition for which an unscheduled procedure was performed, should however be recorded if it meets the definition of an AE. For example, an acute appendicitis should be recorded as the AE and not the appendectomy.

Procedures to support the treatment regimens, such as insertion of central venous catheters etc. should not be recorded as AEs, unless the procedures result in complications.

Events such as lab results reported outside the normal range and determined to be clinically insignificant by the Investigator will not be recorded as AEs.

9.1.2 Adverse Events of Medical Interest

Not applicable.

9.1.3 Expected Adverse Events

Based on pharmacologic action, the following AEs have been observed with Sym004:

- Electrolyte imbalances, including hypomagnesemia, hypocalcemia and hypokalemia
- Dermatological toxicities, acneiform rash, dry skin, fissuring of the skin and secondary skin infections
- Infusion reactions of variable severity

9.1.4 Serious Adverse Event

An SAE is an AE that meets one or more of the following criteria:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in this definition refers to an event in which the patient is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important

NOTE: Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome "Fatal". The death itself will not be reported as an SAE, unless the cause of the death cannot be reported (e.g. in case of unexplained or sudden death).

Events That Do Not Meet the Definition of a Serious Adverse Event

Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be recorded as SAEs, unless an outcome is considered serious.

Hospitalization for observation or convenience following the Sym004/FOLFIRI infusions without an SAE occurring should not be recorded as an SAE, e.g. if a patient is hospitalized merely for observation, or if a patient finalizes the infusion at a time of day requiring a convenience overnight stay in the hospital.

If procedures to support the treatment regimens require hospitalization they should not be recorded as SAEs. However, in cases where a procedure results in complications requiring/prolonging hospitalization this must be recorded and reported as an SAE.

9.2 Adverse Event Recording and Reporting Instructions

9.2.1 Adverse Event Recording Period

All AEs will be recorded from signing the informed consent. The recording period ends at the time of the 1M FUP Visit.

NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.

The Investigator must record all directly observed AEs and all AEs spontaneously reported by the patient. A general, open-ended type of question should be used to elicit a response from the patient, such as, “Do you have any health problems?” or “Have you had any health problems since your last visit?”.

All AEs that occur in patients during the AE recording period must be recorded/entered on the AE section of the Case Report Form (CRF), whether or not the event is assessed as related to Sym004. If the AE is serious, the SAE report forms must also be completed and submitted (see [Section 9.3](#)).

9.2.2 Diagnosis

A diagnosis should be recorded if possible. If no diagnosis is available, signs and symptoms should be recorded instead.

9.2.3 Intensity

The Investigator will use CTCAE version 4.03 to describe the severity of an AE. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death caused by the event

Changes in severity of AEs will be recorded.

Generally, an AE of CTCAE Grade 4 or 5 qualifies for SAE reporting to the Sponsor or designee. However, a laboratory abnormality of CTCAE Grade 4 does not need to be reported as an SAE, unless it meets one of the seriousness criteria in [Section 9.1.4](#).

9.2.4 Relationship to Investigational Medicinal Product/Sym004 and FOLFIRI

The Investigator must assess the AE as either related or not related to the IMP and/or FOLFIRI. Relatedness has to be assessed and recorded within the initial report (CRF and SAE report form).

The causal relationship is an assessment of whether or not the event is related to the use of the IMP and/or FOLFIRI. It is not an evaluation of whether or not the event could hypothetically occur in the investigational patient population.

The causal relationship of an AE to the IMP and/or FOLFIRI will be rated as follows:

Not Related: The AE is not related to the IMP and/or FOLFIRI, which means the event:

- Does not follow a reasonable temporal sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient
- The AE is clearly NOT related to the IMP and/or FOLFIRI

Related: The AE is related to the IMP and/or FOLFIRI, which means the event:

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the IMP and/or FOLFIRI (de-challenge)
- Is confirmed by reappearance of the reaction on repeat exposure (re-challenge)
- Cannot be reasonably explained by the known characteristics of the patient's clinical state
- Is not likely to have been produced by the patient's clinical state or by other modes of therapy administered to the patient

9.2.5 Outcome

Outcome of the AE must be assessed by the Investigator utilizing one of the following terms:

- Recovered
- Recovered with sequelae (if recovered with sequelae, specify sequelae)
- Not recovered
- Fatal
- Unknown

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE CRF pages.

9.2.6 Follow-up of Adverse Events

All AEs should be followed until they are resolved or until the 1M FUP Visit, whichever comes first.

NOTE: Patients who sign Informed Consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.

9.3 Serious Adverse Event Recording and Reporting

All SAEs occurring at any time after the informed consent has been signed and until the 1M FUP Visit, must be recorded on the SAE report form and recorded as an SAE in the CRF.

NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.

In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor or designee. Fax numbers and the e-mail address are stated in the SAE report form and the SAE report form instruction.

Timelines for reporting of SAEs and SAE follow-up information are shown in [Table 18](#).

Table 18 Timelines for Reporting Serious Adverse Events and Follow-up

Type of event	Initial Report		Follow-up Report	
	Time Frame	Document	Time Frame	Document
SAE	24 hours	SAE report form	24 hours	SAE report form

Abbreviation: SAE, Serious Adverse Event

SAEs, still ongoing after 1M FUP Visit, should be followed on a regular basis according to the Investigator's clinical judgment, until the event has been resolved or until the Investigator assesses it as chronic or stable. The Sponsor or designee will pursue sufficient information and will return to the trial sites for such information as deemed required.

If the Investigator becomes aware of an SAE that occurred after the 1M FUP Visit for the patient and finds it related to the IMP or trial conduct it must be recorded and reported to the Sponsor or designee as an SAE. SAEs occurring after the 1M FUP Visit for a patient will not be reported as an SAE in the CRF, i.e. the event will only be recorded in the safety database.

The Investigator should be aware of local reporting regulations to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The Sponsor or designee will either supply the Investigator with the reports, which should be forwarded to the IRB/IEC, or report directly to the IRB/IEC depending on local regulations.

9.4 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

The Sponsor will assess seriousness, causality and expectedness of SAE as reported by Investigator. Expectedness of the event is based on the Reference Safety Information contained within the IB. The Sponsor or designee is responsible for reporting all relevant safety information, including Suspected Unexpected Serious Adverse Reactions (SUSARs), New Safety Issues and annual Development Safety Update Reports, to the Health Authorities (HAs) and to the IRB/IEC concerned. Where applicable as per local requirements, the Investigator will inform the IRB/IEC of the SUSAR.

The Sponsor or designee will inform all Investigators concerned of relevant information about SUSARs.

SUSARs will be reported within 7 days if fatal or life-threatening, otherwise within 15 days.

9.5 Dose-Limiting Toxicities

9.5.1 Definition of Dose-Limiting Toxicities

A DLT is defined as any of the following toxicities that occur during the DLT observation period, if considered by the Investigator, and confirmed by the ISMC, to be related to Sym004 or the Sym004/FOLFIRI combination:

1. Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of:
 - a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤ 5 days with best supportive care
 - b. Grade 3 asymptomatic electrolyte abnormalities¹
2. Any Grade 4 non-hematologic toxicity
3. Neutropenia that is:
 - a. Grade 3 or 4, associated with fever (ANC < 1000 per mm^3 ; temperature $> 38.5^\circ\text{C}$), and requiring antibiotic therapy
 - b. Grade 4 and sustained (i.e., ANC < 500 per mm^3 , duration > 5 days)
4. Thrombocytopenia that is Grade 4 (platelets $< 25,000$ per mm^3)
5. Inability to complete Cycle 1 at the initial assigned doses of Sym004 and FOLFIRI due to \geq Grade 3 toxicity
6. Treatment delays > 2 weeks from the scheduled “next doses” due to \geq Grade 3 toxicity

¹ In addition to the scheduled ECGs (at screening and EOT), an ECG should be performed as soon as possible in the event of \geq Grade 3 hypomagnesemia, and as otherwise clinically indicated. Furthermore, in the event of QT prolongation, an ECG is to be performed prior to the next dose of Sym004. See [Section 7.2.5](#) for further details regarding procedures to address this expected AE.

[Section 12.1](#) outlines the responsibilities of the ISMC with respect to DLTs.

9.5.2 Observation Period for Dose-Limiting Toxicities

Throughout the dose-escalation phase, the decision to dose-escalate is based on close monitoring of safety during the observation period for DLTs, defined as Cycle 1, i.e. the initial 28 day period (± 2 days) from first treatment of Sym004 in combination with FOLFIRI.

A minimum of 2 infusions of Sym004 in combination with FOLFIRI (full doses) must have been administered for a patient to have completed and tolerated the DLT observation period.

9.5.3 Reporting of Dose-Limiting Toxicities

All presumed DLTs must be reported to the Sponsor or designee within 24 hours after the Investigator or designee have become aware of the event. In addition, serious DLTs must be reported in an expedited manner according to the procedure for SAEs, as outlined above.

9.6 Reporting of Infusion-related Reactions

The definition of an IRR is included in [Section 7.1.4.7](#).

All IRRs must be reported in the CRF as an AE with the term “Infusion-related Reaction” followed by a specification of symptoms (e.g. “Infusion-related Reaction with dyspnea and flushing”).

In addition, serious IRRs must be reported in an expedited manner according to the procedure for SAEs, as outlined above.

9.7 Pregnancy

If any trial patient becomes pregnant during the course of the trial, the patient must be discontinued from Sym004 and FOLFIRI immediately and the pregnancy must be reported to the Sponsor or designee according to the same timelines as an SAE. While pregnancy is not considered an AE, all pregnancies are tracked as SAEs within the safety database in order to follow-up on exposure to the fetus/infant.

Pregnancies reported in female partners of male trial patients must also be data-based; therefore, a pregnant partner must provide informed consent before information can be collected.

All pregnancies must be followed up every third month to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate (trial patients only). Elective terminations for non-medical reasons should not be reported as AEs. Spontaneous abortion must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly related to the IMP, must be promptly reported to the Sponsor or designee.

All pregnancy information including follow-up information must be reported in a designated pregnancy form provided by the Sponsor or designee.

10 STATISTICS

10.1 Sample Size Determination

The primary endpoint of the dose-escalation phase is the occurrence of DLTs on each of the Sym004 dose levels given in combination with FOLFIRI. The number of enrolled patients will depend on the extent of observed DLTs independently in each cohort. Please, refer to [Section 7.1.4.2](#) and [7.1.4.3](#) for a description of planned dose levels and decision tree for dose-escalation. Based on a 3 + 3 design, it is planned to enroll between 9 and 18 patients during dose-escalation.

In the dose-expansion phase of the trial, the primary endpoint is confirmed objective antitumor response to the combination of Sym004 and FOLFIRI. The number of patients planned to be included in this part of the trial is 32-41 patients depending on the number of patients enrolled in the dose-escalation phase.

In a Phase III study of patients with CRC treated with a second line regimen including panitumumab plus FOLFIRI, the response rate reported was 35% or 36% ([21](#), [22](#)). In one phase II study of CRC patients treated with cetuximab plus FOLFIRI as a second line regimen, a response rate of 32% was observed ([23](#)). The results from these studies were utilized as references to consider an increment in response rate that would support further studies to evaluate the potential efficacy of the combination of Sym004 and FOLFIRI.

If between 32 and 41 patients are included in the dose-expansion phase of the trial, the lower 90% exact confidence bound of a 47% observed response rate is at least 32%.

10.2 Analysis Populations

Three analysis sets will be defined in accordance with the consolidated ICH E6 GCP guidelines ([1](#)).

The Full Analysis Set (FAS) will comprise all enrolled patients who have received at least one dose of IMP. The FAS will be used for evaluation of safety and PD endpoints. The patients in the FAS will contribute to the analyses as allocated to treatment.

The DLT analysis set will comprise all patients in the FAS. Patients who did not complete Cycle 1 (i.e. minimum 2 infusions of Sym004 in combination with FOLFIRI [full dose]) for reasons other than drug toxicity will be excluded from the DLT analysis set. The DLT analysis set will be used for evaluation of DLTs.

The PK analysis set will comprise all enrolled and exposed patients in the dose-escalation with at least one evaluable PK profile. For a PK profile to be evaluable at least 3 measurements after C_{max} and with a negative slope on the concentration-time curve are required.

The PK analysis set will be used for evaluation of PK. For the evaluation, patients, full profiles, or single measurements can be excluded from the analyses. The decision to exclude patients, full profiles or part of profiles will be described in the Clinical Trial Report (CTR).

10.3 Primary Endpoint and Analysis

10.3.1 Dose Escalation Phase

The primary objective of the dose-escalation phase is to determine the MTD of Sym004, assessed by the occurrence of DLTs during the DLT observation period for each of the Sym004 dose levels given in combination with FOLFIRI.

All DLT events (if any) will be listed by dose cohort and patient. A summary table of DLTs by System Organ Class (SOC) and preferred term will be presented for each dose cohort, if applicable. The summaries will include number of DLTs and number and percentages of patients who experienced a DLT. The definition of a DLT is included in [Section 9.5.1](#). The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD might not be found.

10.3.2 Dose Expansion Phase

The primary objective of the dose-expansion phase is to evaluate the antineoplastic effect of Sym004. This will be evaluated by confirmed OR (i.e. documented PR or CR).

Number and percentages of patients in the FAS with confirmed OR will be presented including corresponding 95% exact Confidence Intervals (CI).

10.4 Secondary Endpoints and Analyses

All statistical analyses of the secondary endpoints for both phases will be performed after completion of the dose expansion phase of the trial.

10.4.1 Safety Endpoints and Analyses

The safety endpoints are presented below and will all be presented for the FAS by trial phase. Safety data will only be presented descriptively, and no formal statistical analyses will be performed.

10.4.1.1 Adverse Events

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) current version. AEs will be regarded as treatment emergent AEs (TEAEs) if they occur after first treatment. Non-treatment emergent AEs (Non-TEAEs) are defined as AEs collected before dosing. TEAEs will be presented by SOC and preferred term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of patients having experienced an event and the total number of events.

AEs including SAEs are reported from signing the informed consent until the end of trial participation. SAEs reported outside the required reporting window are only entered into the safety database and will be described separately in the report.

NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.

All AEs will be listed. The TEAEs will be presented using summary tables by trial phase including:

- AEs, in total and sorted by frequency
- AEs by relationship
- AEs by CTCAE Grade and max CTCAE Grade
- Skin toxicity AEs defined as AEs within a predefined set of preferred terms (list to be included in the Statistical Analysis Plan [SAP])
- AEs of Medical Interest
- SAEs, in total, and by relationship
- AEs leading to withdrawal from treatment
- AEs leading to trial drug interruption or dose reduced
- Fatal AEs

10.4.1.2 Clinical Laboratory Values

Biochemistry, hematology and coagulation parameters will be presented using box plots by visits and by cohort and trial phase. In addition, individual patient biochemistry, hematology and coagulation parameters during the trial will be presented graphically using longitudinal plots. Urinalysis parameters will be summarized using descriptive statistics.

Laboratory values outside normal range by flagged and all laboratory values will be listed including CTCAE grading of abnormal values.

10.4.1.3 Other Assessments Related to Safety

Change in vital signs from baseline to end of trial participation will be summarized by visit, cohort and trial phase. Normal and abnormal findings in physical examination and ECG measurements will be presented in shift tables by visit, cohort and trial phase.

Skin examination will be summarized by visit, cohort and trial phase.

ECOG PS, body weight and ADA results will be listed.

10.4.2 Efficacy Endpoints and Analyses

The following anti-tumor response endpoints will be measured

- Documented OR (dose-escalation)
- Duration of OR from time of first PR or CR to PD
- Changes in sum of diameters of target lesions from baseline to end of trial participation

- SD for > 4 months
- Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first

All secondary efficacy endpoint will be presented using the FAS.

Best overall response by RECIST v1.1 will be summarized by trial phase and dose cohort by means of counts and percentages for the categories CR, PR, SD, PD and NE.

Number and percentages of patients with documented OR in the dose-escalation phase will be presented including corresponding 95% exact CI. All documented ORs (dose-escalation and dose-expansion phase) will be listed including duration of OR.

Duration of SD is calculated from baseline till first measurement of PD. The number and percentages of patients with SD for more than 4 months will be presented by trial phase.

Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first, will be presented using Kaplan-Meier plots by trial phase. The median survival time including 95% CI.

10.4.2.1 Other Efficacy Assessments

CEA will be assessed at Screening, at the end of every even cycle thereafter, and at EOT and 1MFU, if applicable. CEA will be presented using descriptive statistics.

10.4.3 Pharmacokinetic Endpoint and Analyses (Omitted as of Amendment 3)

The PK endpoints will be derived based on the concentration time curves of Sym004, mAb992 and mAb1024, respectively after the first and fourth infusion of Sym004 in the dose-escalation phase, regardless of delays in treatment. Refer to [Table 19](#).

Table 19 PK Endpoints Definitions and Derivations

Symbol	Definition and derivation
$AUC_{0-336h, sym004}$, $AUC_{0-336h, mAb992}$, $AUC_{0-336h, mAb1024}$	Area under the concentration-time curve from time zero (end of infusion) up to 336 hours. AUC_{0-336h} will be calculated using the linear trapezoidal method and interpolated in case of measurements after 336 hours, or extrapolated using terminal rate constant and the last quantifiable concentration, C_z
$AUC_{norm, 0-336h, sym004}$, $AUC_{norm, 0-336h, mAb992}$, $AUC_{norm, 0-336h, mAb1024}$	Dose normalized area under the concentration-time curve from time zero (end of infusion) up to 336 hours, calculated as AUC_{0-336h} divided by the dose infused
$\lambda_z, sym004$, $\lambda_z, mAb992$, $\lambda_z, mAb1024$	Terminal rate constant (negative of the slope of an ln-linear regression of the un-weighted data considering the terminal phase of the concentration-time curve \geq LOQ). λ_z is not an endpoint, but is used for derivation of endpoints

Symbol	Definition and derivation
$CL_{\text{sym004}}, CL_{\text{mAb992}}, CL_{\text{mAb1024}}$	Clearance (Dose/AUC _{0-336h})
$V_{Z_{\text{sym004}}}, V_{Z_{\text{mAb992}}}, V_{Z_{\text{mAb1024}}}$	Volume of distribution during the terminal phase (CL/ λ_z). Formula is used for both profiles as steady state is not reached.
$C_{\text{max, sym004}}, C_{\text{max, mAb992}}, C_{\text{max, mAb1024}}$	Maximum concentration
$C_{\text{trough, sym004}}, C_{\text{trough, mAb992}}, C_{\text{trough, mAb1024}}$	Concentration measured pre-infusion
$T_{\text{max, sym004}}, T_{\text{max, mAb992}}, T_{\text{max, mAb1024}}$	Time of maximum concentration
$T_{1/2, \text{sym004}}, T_{1/2, \text{mAb992}}, T_{1/2, \text{mAb1024}}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$

C_{max} , C_{Trough} and T_{max} will be derived from observed data while AUC_{0-336h}, AUC_{norm, 0-336h}, CL, V_z , and $T_{1/2}$ will be estimated using non-compartmental methods and actual time points.

Individual curves of serum concentration versus time of Sym004, mAb992, and mAb1024, respectively will be presented on log- and linear scale for all patients who have received at least one infusion of Sym004, one plot for each profile after Sym004 administration (the first and fourth infusion) and one plot on linear scale for the whole period of time including trough serum concentrations only. In addition, mean concentration time curves will be presented on linear scale using nominal time point by cohort. Furthermore, the PK endpoints will be summarized by cohort and listed.

10.4.4 Pharmacodynamics Endpoints and Analyses (Omitted as of Amendment 3)

Potential biomarkers includes genes, gene transcripts and proteins of RTKs and molecules of the EGFR signaling pathway. All biomarkers will be listed.

Exploratory analysis using the biomarkers might be performed.

10.5 Interim Analysis

In the dose escalation phase clinical safety data will be assessed when the first patient in a 3-patient cohort has completed and tolerated Cycle 1, when 3 patients have completed and tolerated Cycle 1, and if the cohort is expanded when 6 patients have completed and tolerated Cycle 1.

An ISMC will be established to review all relevant safety and toxicity data of available patients. Please refer to [Section 12](#).

Based on an overall evaluation of the dose-escalation phase, a dose for the second phase of the trial will be recommended by the ISMC, i.e. the RP2D. The RP2D might not necessarily be either the MTD or the highest administered dose.

10.6 Data Collection and Analysis beyond Primary Analysis

As of Amendment 3: After the trial has closed enrollment and all DLT evaluation is completed, the Sponsor may reduce trial data collection to information needed for safety reporting required by the FDA and/or other regulatory authorities, as well as efficacy and safety follow-up data considered necessary by the Sponsor.

10.7 Deviations from the Statistical Plan

Any deviation(s) from the original analysis plan will be described in a CTP Amendment and/or in a SAP and/or in the final CTR, as appropriate.

11 ETHICS

11.1 Independent Ethics Committee or Institutional Review Board

An IEC/IRB will review the CTP and any amendments and advertisements used for recruitment, as well as the informed consent documents, their updates (if any), and any other written materials given to the patients. The CTR will include a list of all IECs/IRBs to which the CTP has been submitted and the name of the committee chair.

11.2 Patient Information and Informed Consent

The Investigator or his/her designee must obtain written informed consent from each patient before any trial related procedures are performed. Each patient must receive full patient information before giving consent. The patient information must contain full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved.

Before signing the informed consent form the patient must be given sufficient time to consider his/her possible participation. Each patient must also be informed about his/her right to withdraw from the trial at any time.

Each patient must sign the informed consent form; the patient receives a copy of the signed form and the original is retained in the Investigator Site File (ISF). The informed consent form must be signed and dated both by the patient and by the Investigator providing the information to the patient.

11.3 Compliance Reference Documents

The trial will be conducted in accordance with the CTP, the principles of the Declaration of Helsinki (18), ICH E6 GCP (1), and other laws in the countries where the trial takes place.

12 SAFETY SURVEILLANCE SET-UP

12.1 Independent Safety Monitoring Committee

An ISMC will be established for the trial. Functions and responsibilities of the ISMC are described in an ISMC charter.

Throughout dose-escalation, the ISMC will review all reported AEs and SAEs on an ongoing basis and will decide by consensus on the following:

- Agreement with the Investigator assessment of a medical event for a patient meeting the DLT definition
- Dose-escalation
- Dose-deescalation
- Dose level expansion (i.e. another 3 patients to be included on a given dose level)
- Suspension of enrollment
- Declaration of the MTD
- Declaration of the R2PD

NOTE: All reported AEs, including those occurring after the end of the DLT observation period, will be considered for decision-making by the ISMC.

Throughout the trial, the ISMC will monitor the overall safety of the trial and provide appropriate recommendations to the Sponsor regarding trial continuation, protocol modifications or trial suspension.

The conclusion of the ISMC meeting will be provided verbally to the Sponsor immediately after each meeting followed by signed written minutes within a few days.

Any safety related ISMC recommendation that may result in protocol changes will be reported to the HAs and IECs/IRBs. A letter of trial continuation after each ISMC meeting will be supplied to IECs/IRBs only if required.

12.2 Other Safety Surveillance Activities

A Medical Monitor is assigned to review and evaluate relevant clinical/safety information concerning the clinical trial. The responsibilities of the Medical Monitor include, but are not limited to

- Evaluation of medical terminology coding and trending of AEs in conjunction with the Drug Safety physician
- Performing surveillance on potential safety signals in conjunction with the Drug Safety physician

- Evaluating abnormal laboratory values
- Providing medical support to the Sponsor in answering questions related to the trial protocol
- Updating the ISMC on trial status at scheduled meetings

A Drug Safety physician is assigned to review, assess and approve all SAE cases and associated reports. This physician will also perform the following:

- Assess for safety signals and trends in conjunction with the Medical Monitor
- Assist with questions regarding coding of SAEs
- Discussing with the Sponsor Chief Medical Officer, any cases which may present a concern with regard to a signal or safety issue.

13 MONITORING AND QUALITY ASSURANCE

13.1 Compliance with Good Clinical Practice

The responsibilities of the Sponsor, the Monitor and the Investigator are defined in ICH E6 GCP (1), and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of the Investigators, and for dispensing IMP only in accordance with this CTP or a signed amendment, and for its storage and safe handling throughout the trial.

13.2 Source Documentation

Each trial site will permit authorized representatives of the Sponsor and relevant authorities to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the trial safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to: Hospital records, clinical and office charts, laboratory notes, memoranda, patients' written diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

The Investigator must maintain source documentations for each patient in the trial and all information in the CRF must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before trial start and will be recorded directly in the CRF, which will be documented as being the source data.

13.3 Monitoring

Monitoring visits to the trial sites will be made periodically during the trial to ensure that the CTP is followed. The Investigator must give the Sponsor and/or their representatives access to all relevant source documents to confirm consistency with the CRF entries and SAEs. Source Data Verification will be conducted according to Sponsor or designee Standard Operating Procedures (SOPs) and requirements will be specified in a trial specific monitoring plan.

It is important that the Investigator and their relevant personnel are available during monitoring visits and possible audits and that sufficient time is devoted to the process.

13.4 Audits and Inspections

Independent audits and inspections of clinical program activities may be performed at any time, before, during and/or after the trial. The Investigator and trial staff is responsible for

maintaining a comprehensive and accurate filing system of all trial-related documentation that will be suitable for inspection at any time by the Sponsor, its designees, and/or HAs. In signing this CTP, the Investigator understands and agrees to give direct access to the necessary documentation and files.

The Sponsor must be notified immediately if HA inspections are announced. For any response forwarded to the authorities that involves a Symphogen sponsored trial, Symphogen must be involved in this correspondence.

14 DATA HANDLING AND RECORD KEEPING

Data will be handled according to good data management practices, all applicable data protection regulations and comply with ICH E6 GCP (1).

14.1 Data Protection

The Investigator, Sponsor and Sponsor designee(s) will ensure that the confidentiality of the patients' data is preserved. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP (1) and regulatory and institutional requirements for the protection of confidentiality of patients.

14.2 Data Transactions and Access

The trial data and any trial document transferred to the Sponsor or designee will not contain patient names or other confidential personal data. Patients will be identified using the assigned trial specific patient numbers.

When data are transferred to the Sponsor or designee, access will be limited to relevant persons.

Documents that are not for collection by the Sponsor, e.g. patient identification list and the signed informed consent forms, will be maintained by the Investigator in confidence.

14.3 Case Report Form

The Investigator or designee will be responsible for entering trial data in the CRF provided. It is the responsibility of the Investigator to ensure the accuracy of the data entered in the CRF.

All collected data will be entered into a validated database.

14.4 Data Processing

The process of entering or uploading of data from trial sites will assure the accuracy of data entry into the database and include a validation at data entry time (real time validation). Entry or electronic transfer of other data than those directly from trial sites (e.g. imports of laboratory results) will follow the Sponsor requirements for data flow and transfer.

The Sponsor or designee will be responsible for data processing in accordance with the applicable data management SOPs.

The Sponsor will ensure that any data management vendor performs the agreed checks on the data quality and manages the query process following their appropriate SOPs in alignment with the requirements as outlined in the relevant Sponsor SOP.

Conduct of medical terminology coding against agreed dictionaries (i.e. MedDRA, WHOdrug and others) forms part of data quality review and database lock. Coding lists will be reviewed and approved by the Sponsor.

Reconciliation of SAEs entered both in the clinical database and in the safety database will be performed before database lock.

All semantically created data will be converted into a CDISC data model.

Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF files of the CRFs will be provided to the investigators at the completion of the trial.

14.5 Retention of Trial Documents at Site

The Investigator at each trial site must make arrangements to store the essential trial documents (including the ISF) after the end of trial according to ICH E6 GCP (1) and local requirements.

In addition, the Investigator is responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial, e.g. in case of inspection from authorities.

The Investigator is required to ensure the continued storage of the documents, even if the Investigator should leave the clinic/practice or retire before the end of the required storage period.

15 REGISTRATION AND COMMUNICATION OF RESULTS

15.1 Use of Information

All unpublished information relating to this trial and the IMP is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator must accept that the Sponsor may use information from this trial in connection with the development of the IMP, and therefore, may disclose it as required to Investigators, to government licensing authorities, to HAs of other government, stock exchange market and commercial partners.

15.2 Registration and Publication

The trial will be registered in one or more public trial registries and results will be reported according to current legislation. The trial results will be posted in the same clinical trial registries as the initial registrations in accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

The Sponsor acknowledges the Investigators' rights to publish the full results of the trial, regardless of the outcome, in accordance with the latest ICMJE recommendations.

The Coordinating Investigator will together with the Sponsor decide on the publication strategy and has the right to publish and present the results and methods as first author of multicenter publications. Co-authorship will be decided by the Sponsor and the Coordinating Investigator and will be limited to a number of persons who have contributed substantially to the trial. The Sponsor will have representation in the list of authors.

Publication is subject to the following conditions:

- No publication before the completion of the trial at all participating trial sites without preceding written approval from the Sponsor
- Publications shall not disclose any Sponsor confidential information and property (not including the trial results)
- The Sponsor reserves the right to review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days. The Sponsor cannot require changes to the communication and cannot extend the embargo

16 INSURANCE AND LIABILITY

The Sponsor will take out Human Clinical Trials Insurance for its legal liability in accordance with laws and regulations, and with limits customary or required by law in the territory in question.

17 CHANGES TO THE FINAL CLINICAL TRIAL PROTOCOL

Changes to the CTP will not be implemented without agreement from the Sponsor and prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the patient. No protocol waivers will be allowed.

18 PREMATURE TERMINATION OF THE TRIAL OR A TRIAL SITE

18.1 Premature Termination of the Trial

If the Sponsor, the Coordinating Investigator or the ISMC discovers conditions arising during the trial, which indicates that the trial should be halted, the trial can be terminated after appropriate consultation between the Sponsor, the ISMC and the Coordinating Investigator. The CA and IEC/IRB will be notified in writing. The reason will be stated.

Conditions that may warrant termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the trial
- The discovery of lack of efficacy
- Failure of the Investigators to enter patients at an acceptable rate in the trial as a whole
- A decision on the part of the Sponsor to suspend or discontinue development of the IMP

18.2 Premature Termination of a Trial Site

The Sponsor can also decide to prematurely terminate single trial sites. Conditions that may warrant termination include, but are not limited to the following:

- Insufficient adherence to CTP requirements
- Failure to enter patients at an acceptable rate

19 REFERENCES

1. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). 10-Jun-1996
2. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. <<http://globocan.iarc.fr>>
3. Brenner H, Kloor M, and Pox CP. Colorectal Cancer. *Lancet*. 2014;383:1490-1502
4. Van Cutsem E, Nordlinger B, and Cervantes A. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. *Ann Oncol*. 2010;21(suppl 5):93-97
5. Davies JM and Goldberg RM. Treatment of metastatic colorectal cancer. *Seminars Oncol*. 2011;38(4):552-560
6. Wolpin BM and Mayer RJ. Systemic treatment of colorectal cancer. *Gastroenterol*. 2008;134(5):1296-1310
7. Kirstein MM, Lange A, Prenzler A, et al. Targeted therapies in metastatic colorectal cancer: a systematic review and assessment of currently available data. *Oncologist*. 2014;19:1156-1168
8. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: Colon cancer. NCCN.org. Version 3.2015
9. Pedersen MW, Jacobsen HJ, Koefoed K, et al. Sym004: a novel synergistic anti-epidermal growth factor receptor antibody mixture with superior anticancer efficacy. *Cancer Res*. 2010;70(2):588-597
10. Koefoed K, Steinaa L, Soderberg JN, et al. Rational identification of an optimal antibody mixture for targeting the epidermal growth factor receptor. *mAbs*. 2011;3(6):584-595
11. Iida M, Brand TM, Starr MM, et al. Sym004, a novel EGFR antibody mixture, can overcome acquired resistance to cetuximab. *Neoplasia*. 2013;15(10):1196-1206
12. Skartved NJO, Jacobsen HJ, Pedersen MW, et al. Preclinical pharmacokinetics and safety of Sym004: a synergistic antibody mixture directed against epidermal growth factor receptor. *Clin Cancer Res*. 2011;17(18):5962-5972
13. Dienstmann R, Patnaik A, Garcia-Carbonero R, et al. Safety and activity of the first-in-class Sym004 anti-EGFR antibody mixture in patients with refractory colorectal cancer. *Cancer Discov*. 2015;5(6):1-12

14. Misale S, Di Nicolantonio F, Sartore-Bianchi A, et al. Resistance to anti-EGFR therapy in colorectal cancer: from heterogeneity to convergent evolution. *Cancer Discov.* 2014;4(11):1269-1280
15. Rajput A, Koterba AP, Kreisberg JI, et al. A novel mechanism of resistance to epidermal growth factor receptor antagonism in vivo. *Cancer Res.* 2007;67(2):665-673
16. Argilés G, Dienstmann R, Viñuales MB, et al. Phase 1 study of biweekly (Q2W) anti-EGFR monoclonal antibody (mAb) mixture Sym004 in patients (pts) with metastatic colorectal cancer (mCRC) resistant to previous anti-EGFR treatment. 2014 ASCO Annual Meeting, General Poster Session, Gastrointestinal (Colorectal) Cancer. <http://meetinglibrary.asco.org/content/127412-144>
17. Machiels J-P, Specenier P, Krauß J, et al. A proof of concept trial of the anti-EGFR antibody mixture Sym004 in patients with squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol.* 2015;76(1):13-20
18. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA.* 2013;310(20):2191-2194
19. American Heart Association. Classification of Functional Capacity and Objective Assessment. http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp
20. Annex 13 to Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. 03 February 2010
21. Peeters M, Price TJ, Cervantes A, et al. Final results from a randomized phase 3 study of FOLFIRI +/- panitumumab for second-line treatment of metastatic colorectal cancer. *Annals of Oncology.* 2014;25:107-116
22. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS Mutations in a Phase 3 Study of Panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Cancer Research.* 2015;21:5469-5479
23. Iwamoto S, Hazama S, Kato HS, et al. Multicenter phase II study of second-line Cetuximab plus Folinic Acid/5-Fluorouracil/Irinotecan (FOLFIRI) in KRAS wild-type metastatic colorectal cancer: The FLIER Study. *Anticancer Research.* 2014;34:1967-1974

20 APPENDICES

Appendix 1 Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

For details, see Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247.

Measurability of tumor at baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on “Baseline documentation of target and non-target lesions” for information on lymph node measurement.

Non-measurable:

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment

- Tumor lesions situated in a previously irradiated area, or other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules).

For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans)
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in [Table 20](#) and [Table 21](#).

Table 20 Response Criteria for Evaluation of Target Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (NOTE: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Table 21 Response Criteria for Evaluation of Non-target Lesions

	Evaluation of Non-target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (NOTE: the appearance of one or more new lesions is also considered progression)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Evaluation of Best Overall Response

It is assumed that at each protocol specified time point, a response assessment occurs.

Table 22 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 22 Overall Response Status for Patients with Baseline Measurable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR IS NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient’s best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered non-evaluable.

Best response determination in trials where confirmation of CR or PR IS required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in [Table 23](#).

Table 23 Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR ¹
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

- 1) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes ‘CR’ may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 2 FOLFIRI Guidelines for Dose Modifications and Delays

The following sections include guidelines for dose modifications and delays associated with specific symptoms.

Neutropenia or Thrombocytopenia

The following guidelines are based on the worst grade of neutropenia or thrombocytopenia observed during a 2-week dosing period (*Please note: For the purposes of this trial, two consecutive 2-week dosing periods equals 1 cycle*):

- Grade 2 neutropenia or thrombocytopenia: 5-FU and irinotecan may be resumed at the previous dose levels for the next administration, provided ANC $\geq 1.5 \times 10^3/\mu\text{L}$ ($1.5 \times 10^9/\text{L}$) and platelets $\geq 100 \times 10^3/\mu\text{L}$ ($100 \times 10^9/\text{L}$). If hematologic criteria are not met, doses of 5 FU and irinotecan should be reduced for the next administration.
- Grade 3 or 4 neutropenia or thrombocytopenia: Interrupt or skip 5-FU and irinotecan. Skipped doses are not to be made up. For subsequent administrations, 5-FU and irinotecan should continue at 1 dose level lower.
- Febrile neutropenia (ANC $< 1.0 \times 10^3/\mu\text{L}$ [$1.0 \times 10^9/\text{L}$] and fever $\geq 38.5^\circ\text{C}$): Interrupt or skip 5-FU and irinotecan. If fever resolves, neutropenia resolves to ANC $\geq 1.5 \times 10^3/\mu\text{L}$ ($1.5 \times 10^9/\text{L}$), and platelets are $\geq 100 \times 10^3/\mu\text{L}$ ($100 \times 10^9/\text{L}$), 5-FU and irinotecan should continue at 1 dose level lower for the next administration. Skipped doses are not to be made up.

If a dose delay is required due to any grade of neutropenia or thrombocytopenia, prophylactic use of granulocyte colony-stimulating factor (G-CSF)/granulocyte macrophage colony stimulating factor (GM-CSF) prior to the next administration of FOLFIRI is permitted at investigator discretion, provided that G-CSF/GM-CSF administration is completed ≥ 48 hours prior to administration of FOLFIRI.

Diarrhea

Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25 to 1.0 mg IV or subcutaneously, may be used (unless clinically contraindicated) to treat these symptoms at the discretion of the treating physician. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia).

Late diarrhea (developing more than 24 hours after irinotecan) should be managed with loperamide. Refer to [Table 8](#) for mandatory prophylaxis for diarrhea.

Dose modifications in this section are based on the worst grade of diarrhea experienced during a 2-week dosing period:

- Grade 2: For the next administration, 5-FU should be continued at 1 dose level lower, provided diarrhea has recovered to Grade ≤ 1 . For recurrent Grade 2 diarrhea, both 5-FU and irinotecan should be continued at 1 dose level lower for the next administration.
- Grade 3: Interrupt or skip 5 FU and irinotecan. If diarrhea resolves to Grade ≤ 1 during the current 2-week dosing period, 5-FU and irinotecan administration may be resumed at 1 dose level lower for the next administration. Skipped doses are not to be made up. For subsequent administrations, 5 FU and irinotecan should continue at the reduced dose levels.
- Grade 4: Interrupt or skip 5-FU and irinotecan. If Grade 4 diarrhea does not resolve to Grade ≤ 1 during the current 2-week dosing period, 5-FU and irinotecan administration should be held for another 2-week period (approximately 28 days) until resolution to Grade ≤ 1 ; when treatment resumes, the doses of 5-FU and irinotecan should be reduced by 2 dose levels.

Mucositis

The following guidelines are based on the worst grade of mucositis observed during a 2-week dosing period:

- Grade 2: If mucositis resolves to Grade ≤ 1 during the current 2-week dosing period, 5-FU may be continued at the same dose level or may be resumed at 1 dose level lower during the next administration. For recurrent Grade 2 mucositis, the dose of 5-FU should be reduced by an additional dose level.
- Grade 3: If mucositis resolves to Grade ≤ 1 during the current 2-week dosing period, 5-FU may be resumed at 1 dose level lower for the next administration. If mucositis does not resolve to Grade ≤ 1 during the current 2-week dosing period, 5 FU administration should be held for another 2-week dosing period (approximately 28 days) until resolution to Grade ≤ 1 ; when treatment resumes, the dose of 5-FU should be reduced by 2 dose levels.
- Grade 4: Interrupt or skip 5-FU and irinotecan. 5-FU administration should be held for a maximum of 1 cycle (approximately 28 days) until resolution to Grade ≤ 1 ; when treatment resumes, the dose of 5-FU should be reduced by 2 dose levels.

Nausea/Vomiting

The following guidelines are based on the worst grade of nausea and vomiting occurring during a 2-week dosing period. Dose reductions should occur only if symptoms persist despite 2 treatments with adequate (combination) antiemetic treatment. Note that the irinotecan prescribing information recommends that patients receive premedication with antiemetic agents.

- Grade 3: Reduce irinotecan 1 dose level for the next administration. Continue irinotecan at the reduced dose level for subsequent administrations.
- Grade 4: Reduce 5-FU and irinotecan 1 dose level for the next administration. Continue both 5 FU and irinotecan at the reduced dose levels for subsequent administrations.

Skin Toxicity

Dose modifications in this section are based on the worst grade of skin toxicity experienced during a 2-week dosing period. For Grade 3 or 4 skin toxicity, interrupt or skip 5 FU. 5-FU should be held for a maximum of 1 cycle (approximately 28 days) until resolution to Grade ≤ 1 ; when treatment resumes, the dose of 5-FU should be reduced by 2 dose levels.

Cardiac Toxicity

In the event of Grade ≥ 2 cardiac toxicity attributable to 5-FU, treatment with 5-FU should be discontinued.

Other Nonhematologic Toxicity

For Grade ≥ 3 nonhematologic toxicities not described above, withhold treatment with FOLFIRI and monitor toxicity at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, treatment may be resumed with 5-FU and irinotecan at 1 dose level lower. For Grade 3 toxicities associated primarily with laboratory abnormalities only (for example, elevation of ALT, AST, hyperlipasemia, hyperamylasemia, hypophosphatemia without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment may continue without interruption at the discretion of the investigator.

Neurocerebellar Toxicity

In the event of neurocerebellar toxicity, treatment with 5-FU should be discontinued.

21 SUMMARY OF CHANGES

21.1 Protocol Amendment 1 dated 09-Nov-2015

1. Increase the blood volume collected for the biomarker
2. Change timing for collecting AEs/SAEs
3. Correction and clarification of inconsistencies and minor typographical errors

The objective of the present amendment is to increase the volume of blood for biomarker analysis from 5mL to 20mL per blood sample collection. The blood sample is collected from patients at screening, end of cycle 2 or upon disease progression (whichever occurs first), and at the end of trial. A larger volume of blood, and subsequent plasma, is needed for biomarker analysis when using Next-Generation Sequencing (NGS).

Timing for collection of AEs and SAEs is being extended. This will 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.

Minor typographical errors and inconsistencies have been corrected.

With reference to “Detailed Guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of trial (CT-1)” paragraph, this amendment is considered substantial as it has an impact on the conduct or management of the trial.

Refer to [Table 24](#) for the changes in Protocol Amendment 1.

Table 24 Protocol Amendment 1 dated 09-Nov-2015

SECTION	CHANGE	ORIGINAL TEXT	NEW TEXT
Section: 1 Heading: List of Abbreviations and Definitions of Terms	Addition		TEAE: Treatment Emergent Adverse Events
Section: 5.3.5 Heading: Table 2 Flow Chart – Schedule of Assessments Day within Cycle Visit Window (\pm days)	Correction	Cycle 2, 4, 6 etc. D1 (\pm 2) Cycle 3, 5, 7 etc. D1 (\pm 2)	Cycle 2, 4, 6 etc. D1 (\pm 2) Cycle 3, 5, 7 etc. D1 (\pm 2)
Section: 5.3.5 Heading: Table 2 Flow Chart – Schedule of Assessments (S)AE Survey and Reporting	Addition	(S)AE survey and Reporting collected from C1D1	(S)AE survey and Reporting collected from C1D1 Screening

SECTION	CHANGE	ORIGINAL TEXT	NEW TEXT
Section: 7.1.5.1 Heading: Sym004 Dose-Adjustments for Body Weight Sentence: 2	Clarification	The dose calculated may be used for subsequent infusions, unless body weight changes $\geq \pm 5\%$	The dose calculated may be used for subsequent infusions, unless body weight changes $\geq \pm 5\%$ <i>from screening</i>
Section: 8.2.2 Heading: Adverse Event Survey Bullet point: 1	Addition	Starting from the first dose of Sym004 (C1/D1)	Starting from the first dose of Sym004 (C1/D1) <i>signing the informed consent</i>
Section: 8.2.6 Heading: Physical Examination Sentence: 1	Correction	To be performed by a physician. To include evaluation of	To be performed by a physician. To include evaluation of
Section: 8.6 Heading: Biomarker Blood and Urine Sample Paragraph 3 Sentence 1	Correction	Patients will have blood samples taken of approximately of 5 mL	Patients will have blood samples taken of approximately of 5 20 mL
Section: 9.2.1 Heading: Adverse Event Recording Period Sentence: 1	Addition	All AEs will be recorded from the initiation of Sym004 dosing	All AEs will be recorded from the initiation of Sym004 dosing <i>signing the informed consent</i>
Section: 9.3 Heading: Serious Adverse Event Recording and Reporting Sentence: 1	Addition	All SAEs occurring at any time after the first dose of Sym004	All SAEs occurring at any time after the first dose of Sym004 <i>informed consent has been signed</i>
Section: 10.4.1.1 Heading: Adverse Events Paragraph: 1 Sentence: 1 and 2	Addition	The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) current version and presented by SOC and preferred term unless stated otherwise. The frequencies of AEs will be presented including number and percentages of patients having experienced an event and the total number of events.	The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) current version. AEs will be regarded as treatment emergent AEs (TEAEs) if they occur after first treatment. Non-treatment emergent AEs (Non-TEAEs) are defined as AEs collected before dosing. And TEAEs will be presented by SOC and preferred term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of patients having experienced an

SECTION	CHANGE	ORIGINAL TEXT	NEW TEXT
			event and the total number of events.
Section: 10.4.1.1 Heading: Adverse Events Paragraph: 2 Sentence: 1	Addition	AEs including SAEs are reported from first treatment until the end of trial participation	AEs including SAEs are reported from first treatment <i>signing the informed consent</i> until the end of trial participation
Section 10.4.1.1 Heading: Adverse Events Paragraph: 3 Sentence: 1	Addition	All AEs will be listed. The AEs will be presented using summary tables by trial phase including:	All AEs will be listed. The <i>TEAEs</i> will be presented using summary tables by trial phase including:

Amended text are ~~struck through~~ with a single line and new text is written *in italics*

21.2 Protocol Amendment 2 dated 05-Aug-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

The objective of Amendment 2 is to add additional dose levels to facilitate further exploration of the safety and tolerance of lower doses of Sym004 in combination with FOLFIRI, if necessary.

Because of the safety and tolerability observed in patients entered in the initial cohort (Dose Level 1: 12 mg/kg Sym004 + FOLFIRI), mandatory prophylaxis for diarrhea has been added for all patients during Cycle 1, with the potential to continue based on the Investigator's discretion.

Sym004 dose adjustment for obese patients has been removed until there is sufficient data to support it. Symphogen is in the process of completing a population pharmacokinetics model based on data from completed studies.

Clarified that the RP2D will be based on the MTD, toxicities observed during Cycle 1 and subsequent cycles, as well as PK and other relevant data.

Minor modifications, clarifications, and specifications have been added, and minor typographical errors and inconsistencies have been corrected.

Refer to [Table 25](#) for the changes in Protocol Amendment 2.

Table 25 Protocol Amendment 2 dated 05-Aug-2016

SECTION	ORIGINAL TEXT	NEW TEXT
2. Synopsis Diagnosis and Main Inclusion and Exclusion Criteria	<p><u>Main Inclusion Criteria include:</u> Failed* treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab, during treatment or < 3 months after the last dose of first-line therapy and within < 3 months of C1/D1. Patients who discontinued first-line therapy due to toxicity may be enrolled provided progression occurred < 6 months after the last dose of the first-line therapy regimen. or Failed* adjuvant therapy with combination therapy of oxaliplatin and a fluoropyrimidine during treatment or within < 6 months after the last dose of oxaliplatin and within < 6 months of C1/D1.</p>	<p><u>Main Inclusion Criteria include:</u> Failed* prior treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab. Patients who discontinued first-line therapy due to toxicity and who subsequently progressed may be enrolled. or Failed* adjuvant therapy with combination therapy of oxaliplatin and a fluoropyrimidine.</p> <p><u>Main Exclusion Criteria include:</u></p> <ul style="list-style-type: none"> Discontinuation of prior therapy with oxaliplatin and a fluoropyrimidine due to diarrhea ≥ Grade 3
2. Synopsis Investigational Medicinal Product, Dose(s) and Treatment Schedule	<p>If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, a successive lower dose levels will be explored: • Dose Level -1: Sym004 9 mg/kg + FOLFIRI</p>	<p>If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, successive lower dose levels will be explored:</p> <ul style="list-style-type: none"> Dose Level -1: Sym004 9 mg/kg + FOLFIRI Dose Level -2: Sym004 9 mg/kg (loading dose) + FOLFIRI followed by 6 mg/kg + FOLFIRI Dose Level -3: Sym004 6 mg/kg + FOLFIRI <p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) has not exceeded the MTD and is well tolerated during Cycle 1, but overall tolerability is judged to be</p>

SECTION	ORIGINAL TEXT	NEW TEXT
		<p>insufficient to accept this dose level as the RP2D, then Dose Level -2 may be explored.</p> <p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) during Cycle 1 has not exceeded the MTD, but tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose-Level -3 may be explored</p> <p>If the toxicity profile of lower doses where mandatory diarrhea prophylaxis is utilized indicates that the dose is well tolerated, further evaluation of Dose Level 1, and potentially Dose Levels 2 and 3 may take place after approval by the ISMC.</p>
3.2.1 Sym004	Each mAb is manufactured by Chinese Hamster Ovary cells (referred to as CHO cells), transfected with an expression vector coding for both the antibody light chains and heavy chains.	<i>Removed</i>
5.1 Overall Design and Plan	Patients will be allocated in sequence to 1 of up to 3 dose levels of Sym004. The MTD is expected to be found and a RP2D will be declared. The MTD and RP2D may or may not be the same.	Patients will be allocated in sequence to 1 of up to 5 dose levels of Sym004, based on tolerability. The RP2D will be based on the MTD evaluation as well as other toxicities observed in the study, and may include tolerability observed in Cycle 1 and subsequent cycles as well as PK and other data. The MTD and RP2D may or may not be the same, and the RP2D may be selected based on overall tolerability without defining the MTD.
5.3.1 Screening	<i>Not applicable</i>	In the event a tumor biopsy is required for eligibility, informed consent may be obtained outside the 14-day screening period prior to C1/D1 to allow adequate turnaround time for receipt of results.
5.3.5 Flow Chart – Schedule of Assessments (Table 2 footnotes)	<p>5. Local laboratory results must be available and assessed prior to each Sym004/FOLFIRI infusion.</p> <p>8. Tumor Marker, Carcinoembryonic Antigen (CEA), and/or Carbohydrate Antigen 19-9 (CA 19-9).</p> <p>15. Patients will receive prophylactic treatment for FOLFIRI induced diarrhea</p>	<p>5. Local laboratory results must be available and assessed no later than 2 days prior to each Sym004/FOLFIRI infusion.</p> <p>8. Tumor Marker, Carcinoembryonic Antigen (CEA).</p> <p>15. Patients will receive prophylactic treatment for nausea and vomiting</p>

SECTION	ORIGINAL TEXT	NEW TEXT
	and vomiting according to institutional standards.	according to institutional standards, and all patients will be treated with loperamide in an effort to prevent diarrhea during Cycle 1. Prophylaxis with loperamide may be continued beyond Cycle 1 at the Investigator's discretion.
6.1 Inclusion Criteria All Cohorts	<p>6. Failed* treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab, during treatment or < 3 months after the last dose of first-line therapy and within < 3 months of C1/D1.</p> <p>Patients who discontinued first-line therapy due to toxicity may be enrolled provided progression occurred < 6 months after the last dose of the first-line therapy regimen.</p> <p>or</p> <p>Failed* adjuvant therapy with combination therapy of oxaliplatin and a fluoropyrimidine during treatment or within < 6 months after the last dose of oxaliplatin and within < 6 months of C1/D1.</p>	<p>6. Failed* prior adjuvant therapy or prior treatment for locally advanced or metastatic disease with first-line combination therapy of oxaliplatin and a fluoropyrimidine, with or without bevacizumab.</p>
6.2 Exclusion Criteria All Cohorts	<p><i>Not applicable</i></p> <p>6. Drugs with the potential to cause QT prolongation within 2 weeks prior to C1/D1</p> <p>13. Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism within 6 months prior to C1/D1</p>	<p>4. Discontinuation of prior therapy with oxaliplatin and a fluoropyrimidine due to diarrhea \geq Grade 3</p> <p><i>Removed</i></p> <p>13. Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 4 weeks prior to C1/D1; any prior thrombosis must be adequately treated and stable</p>
7.1.4.2 Dose- Escalation Phase	<p>If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, a successive lower dose level will be explored:</p> <ul style="list-style-type: none"> • Dose Level -1: Sym004 9 mg/kg + FOLFIRI 	<p>If the toxicity profile of Dose Level 1 indicates that this dose is not tolerated, successive lower dose levels will be explored:</p> <ul style="list-style-type: none"> • Dose Level -1: Sym004 9 mg/kg + FOLFIRI • Dose Level -2: Sym004 9 mg/kg (loading dose) + FOLFIRI followed by 6 mg/kg + FOLFIRI

SECTION	ORIGINAL TEXT	NEW TEXT
		<p>• Dose Level -3: Sym004 6 mg/kg + FOLFIRI</p> <p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) has not exceeded the MTD and is well tolerated during Cycle 1, but overall tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose Level -2 may be explored.</p> <p>If Sym004 at 9 mg/kg + FOLFIRI (Dose-Level -1) during Cycle 1 has not exceeded the MTD, but tolerability is judged to be insufficient to accept this dose level as the RP2D, then Dose-Level -3 may be explored</p> <p>If the toxicity profile of lower doses where mandatory diarrhea prophylaxis is utilized indicates that the dose is well tolerated, further evaluation of Dose Level 1, and potentially Dose Levels 2 and 3 may take place after approval by the ISMC.</p>
7.1.4.3 Dose-Escalation Decision Points	NOTE: Should ≥ 2 of 6 patients at Dose Level 1 experience a DLT, then the dose will be de-escalated to Dose Level -1.	NOTE: Should ≥ 2 of 6 patients at Dose Level 1 experience a DLT, then the dose will be reduced to Dose Level -1. Furthermore, if ≥ 2 of 6 patients at Dose Level -1 experience a DLT, then the dose will be reduced to Dose Level -3.
7.1.4.8 Handling of Infusion-Related Reactions Table 5: Infusion-Related Reactions Management Guidelines	<p>Grade 2: Stop Sym004 infusion</p> <p>Grade 3: Stop Sym004 infusion</p> <p>Withdraw the patient from treatment</p>	<p>Grade 2: Interrupt Sym004 infusion for a minimum of 30 minutes</p> <p>Grade 3: Discontinue Sym004 infusion</p> <p>Either withdraw the patient from treatment or continue subsequent treatments at a reduced dose</p> <p>Premedication should be reinstated if previously discontinued</p>
7.1.5 Dose-Adjustments and Delays of Sym004	Weight changes ($\geq \pm 5\%$) for a patient during trial will require recalculation of the dose (Section 7.1.5.1).	Weight changes ($\geq \pm 10\%$) for a patient during trial will require recalculation of the dose (Section 7.1.5.1).

SECTION	ORIGINAL TEXT	NEW TEXT
	<p>Dose-adjustments are required for obese patients (Section 7.1.5.2).</p> <p>Furthermore, dose omissions of Sym004 and intra-patient dose-reduction(s) may also be required upon occurrence of Grade 3 anti-EGFR-associated skin toxicity (Section 7.1.5.3) and other safety events (Section 7.1.5.4).</p>	<p><i>Removed</i></p> <p>Furthermore, dose delays of Sym004 and intra-patient dose-reduction(s) may also be required upon occurrence of Grade 3 anti-EGFR-associated skin toxicity (Section 7.1.5.2) and other safety events (Section 7.1.5.3). Dose adjustments should be discussed with the Sponsor or designee prior to implementation.</p> <p>If Sym004 administration is delayed, subsequent dosing will be resumed in combination with a scheduled FOLFIRI administration.</p>
<p>7.1.5.1 Sym004 Dose-Adjustments for Body Weight</p>	<p>The dose calculated may be used for subsequent infusions, unless body weight changes $\geq \pm 5\%$ from screening, in which case the dose must be adjusted according to the change in body weight.</p>	<p>The dose calculated may be used for subsequent infusions, unless body weight changes $\geq \pm 10\%$ from screening, in which case the dose must be adjusted according to the change in body weight. Adjustment may be made in the event of lesser incremental changes in weight at the site's discretion.</p>
<p>7.1.5.2 Sym004 Dose-Adjustments for Obese Patients</p>	<p>If the Body Mass Index (BMI) of a patient exceeds 30 kg/m², the dose of Sym004 must be adjusted according to the following algorithm: Adjusted dose (mg) = 30 (kg/m²) × height² (m²) × planned dose (mg/kg)</p> <p>Example: Planned dose: 12 mg/kg Patient metrics: Weight 90.0 kg, height of 1.62 m, giving a BMI = Body weight (kg) / height² (m²) = 90 kg / 1.62² m² = 34.3 kg/m² The adjusted dose to be administered according to the algorithm provided is: 30 kg/m² × (1.62 m)² × 12 mg/kg = 944.8 mg</p>	<p><i>Entire section removed</i></p>
<p>7.2.3.2 Prophylactic Treatment for Gastrointestinal Toxicities</p>	<p>To minimize the risk of side-effects related to FOLFIRI, all patients will receive:</p> <ul style="list-style-type: none"> • Prophylactic treatment for diarrhea and vomiting according to institutional standards 	<p>To minimize the risk of gastrointestinal side-effects related to FOLFIRI and/or Sym004, all patients will receive:</p> <ul style="list-style-type: none"> • Prophylaxis for nausea and vomiting according to institutional standards • Mandatory prophylaxis for diarrhea as shown in Table 8. Loperamide therapy

SECTION	ORIGINAL TEXT	NEW TEXT
		may be continued beyond end of Cycle 1 (C1) at the Investigator's discretion.
7.5.2 Prohibited Concomitant Medication/Therapy and Procedures during the Trial	Drugs with the potential to cause QT prolongation	<i>Removed</i>
8.1.1 Signing of Informed Consent	<i>Not applicable</i>	NOTE: In the event a tumor biopsy is required for eligibility, informed consent may be obtained outside the 14-day screening period prior to C1/D1
8.2.2 Adverse Event Survey	<i>Not applicable</i>	NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial
8.2.7 Dermatological Assessment	To be performed by a physician; complete skin examination	To be performed by a physician or qualified designee; complete skin examination
8.2.8 Electrocardiogram	<i>Not applicable</i>	In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.
8.3.1 Tumor Marker Evaluation	To include Carcinoembryonic Antigen (CEA) and/or Carbohydrate Antigen 19-9 (CA19-9). Will be performed at a laboratory facility local to the trial site	To include Carcinoembryonic Antigen (CEA). Will be performed at a laboratory facility local to the trial site
8.3.2 Disease Status Evaluation using CT or MRI	Patients will undergo imaging of the thorax and abdomen by CT or MRI.	Patients will undergo imaging of the thorax, abdomen, and pelvis by CT or MRI as indicated, based on tumor type and prior areas of documented disease.
8.6.2 Fresh Tumor Biopsy Collection	<i>Not applicable</i>	Biomarker testing from collected tumor biopsies (archival FFPE or fresh tumor biopsy) will, if amount allows, in addition to RAS and EGFR, include biomarkers connected to EGFR signaling or escape mechanisms observed after EGFR treatment.
9.1.1 Adverse Event	<i>Not applicable</i>	Events such as lab results reported outside the normal range and determined to be clinically insignificant by the Investigator will not be recorded as AEs.

SECTION	ORIGINAL TEXT	NEW TEXT
9.2.1 Adverse Event Reporting Period	<i>Not applicable</i>	NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.
9.2.3 Intensity	The grade assigned by the Investigator should be the most severe that occurred during the AE period.	Changes in severity of AEs will be recorded.
9.2.6 Follow-up of Adverse Events	<i>Not applicable</i>	NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.
9.3 Serious Adverse Event Recording and Reporting	<i>Not applicable</i>	NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.
9.5.1 Definition of Dose-limiting Toxicities	<p>a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤ 2 days with best supportive care</p> <p>b. Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not considered clinically relevant by the Investigator and that resolve with medical therapy</p>	<p>a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤ 5 days with best supportive care</p> <p>b. Grade 3 asymptomatic electrolyte abnormalities¹</p> <p>¹In addition to the scheduled ECGs (at screening and EOT), an ECG should be performed as soon as possible in the event of \geq Grade 3 hypomagnesemia, and as otherwise clinically indicated. Furthermore, in the event of QT prolongation, an ECG is to be performed prior to the next dose of Sym004. See Section 7.2.5 for further details regarding procedures to address this expected AE.</p>
9.5.3 Reporting of Dose-Limiting Toxicities	All presumed DLTs must be reported in the eCRF within 24 hours after the Investigator or designee have become aware of the event.	All presumed DLTs must be reported to the Sponsor or designee within 24 hours after the Investigator or designee have become aware of the event.
10.1 Sample Size Determination	The planned number of patients to be enrolled is not based on a formal sample size calculation. In trial Sym004-01 a total of 3 out of 91 patients had confirmed objective tumor response.	In a Phase III study of patients with CRC treated with a second line regimen including panitumumab plus FOLIFIRI, the response rate reported was 35% or 36% (22, 23). In one phase II study of

SECTION	ORIGINAL TEXT	NEW TEXT
	Based on this it is expected to observe 1-2 patients with confirmed CR or PR in the current trial.	CRC patients treated with cetuximab plus FOLFIRI as a second line regimen, a response rate of 32% was observed (24). The results from these studies were utilized as references to consider an increment in response rate that would support further studies to evaluate the potential efficacy of the combination of Sym004 and FOLFIRI. If between 32 and 41 patients are included in the dose-expansion phase of the trial, the lower 90% exact confidence bound of a 47% observed response rate is at least 32%.
10.4.1.1 Adverse Events	<i>Not applicable</i>	NOTE: Patients who sign the informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined they will not be participating in the trial.
10.4.2.1 Other Efficacy Assessments	CEA and/or CA19-9 will be assessed at Screening, at the end of every even cycle thereafter, and at EOT and 1MFU, if applicable. CEA and CA19-9 will be presented using descriptive statistics.	CEA will be assessed at Screening, at the end of every even cycle thereafter, and at EOT and 1MFU, if applicable. CEA will be presented using descriptive statistics.
Appendix 2: FOLFIRI Guidelines for Dose Modifications and Delays Mucositis	Grade 2: If mucositis resolves to Grade ≤ 1 during the current 2-week dosing period, 5-FU should be continued at the dose level lower during the next administration.	Grade 2: If mucositis resolves to Grade ≤ 1 during the current 2-week dosing period, 5-FU may be continued at the same dose level or may be resumed at 1 dose level lower during the next administration.

21.3 Protocol Amendment 3 dated 22-Feb-2017

The objectives of Amendment 3 are to stop the enrollment of the trial and to change the total scope of assessments being conducted as a result of a Sponsor decision to discontinue the development of Sym004 in combination with FOLFIRI.

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.

Refer to [Table 26](#) for the changes in Protocol Amendment 3.

Table 26 Protocol Amendment 3 dated 22-Feb-2017

SECTION	ORIGINAL TEXT	NEW TEXT
2. Synopsis: Trial Sites and Countries 5.1 Overall Design and Plan	Dose-escalation: 2-3 investigational trial sites	Dose-escalation: Approximately 8 investigational trial sites
2. Synopsis: Objectives 4.1 Dose-Escalation (Phase 1b)	<i>Not applicable</i>	As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, the primary, secondary, and exploratory objectives are no longer applicable. Clinical safety-related evaluations will continue to be conducted.
2. Synopsis: Endpoints 4.4 Trial Endpoints	<i>Not applicable</i>	As of Amendment 3: Due to the premature discontinuation of the enrollment of the trial, only the clinical safety-related evaluations will continue to be conducted.
2. Synopsis: Design and Plan 3.3 Trial Rationale	<i>Not applicable</i>	<p>As of Amendment 3: This amendment to the clinical trial protocol (CTP) is based on a Sponsor decision to discontinue the development of Sym004 in combination with FOLFIRI. As a result, enrollment has stopped and a reduction in the total scope of non-safety related assessments being conducted under this CTP will be implemented.</p> <p>Patients who are actively being treated with Sym004 alone or in combination with FOLFIRI may continue therapy until unacceptable toxicity or other conditions preventing further administration, progressive disease (PD), or patient's decision to withdraw. <u>Patients no longer receiving Sym004 alone or in combination with FOLFIRI should be discontinued from study participation.</u></p> <p>Patients will continue to be followed and assessed for clinical safety-related concerns throughout their respective treatment periods and at minimum for 30 days after the last administration of Sym004.</p>

SECTION	ORIGINAL TEXT	NEW TEXT
2. Synopsis: Criteria for Evaluation	<p>Additional Assessments</p> <ul style="list-style-type: none"> Pharmacokinetic (PK) Sampling Anti-Drug Antibody (ADA) Testing Biomarker blood and urine sample 	<p>Additional Assessments</p> <ul style="list-style-type: none"> Pharmacokinetic (PK) Sampling* Anti-Drug Antibody (ADA) Testing* Biomarker blood and urine sample* <p>*Omitted with Amendment 3</p>
5.1 Overall Design and Plan: Treatment Period	<i>Not applicable</i>	As of Amendment 3: The visit schedule for the treatment period will apply until Sym004 has been discontinued.
5.3.3 Treatment		
5.1 Overall Design and Plan: End of Treatment/Follow-up	<i>Not applicable</i>	As of Amendment 3: Once Sym004 has been discontinued, an EOT Visit will be performed within 10 days from the decision to withdraw treatment, and a follow-up visit will be performed 1 month after the last administration of Sym004.
5.3 Schedule of Events: Table 1	<i>Not applicable</i>	As of Amendment 3: The schedule for the treatment period will apply from the initiation of Sym004 and FOLFIRI until Sym004 has been discontinued. An EOT Visit will be performed within 10 days from the decision to withdraw treatment with Sym004, and a follow-up visit will be performed 1 month after the last administration of Sym004.
5.3.4 End of Treatment and One Month Follow-up Visit	<i>Not applicable</i>	As of Amendment 3: An EOT Visit will be performed for all patients within 10 days after the decision to discontinue treatment with Sym004. The patient will return for follow-up 1 month after the last administration of Sym004.
5.3.5 Flow Chart – Schedule of Assessments	<p><u>Additional Assessments:</u> PK Samples (dose-escalation only) ADA Sample Biomarker Blood and Urine Sample</p> <p>Footnote 1: The treatment phase continues until the patient is withdrawn from trial treatments (i.e. Sym004 and all components of FOLFIRI)</p>	<p><u>*Additional Assessments:</u> *PK Samples (dose-escalation only) *ADA Sample *Biomarker Blood and Urine Sample *Omitted with Amendment 3</p> <p>Footnote 1: The treatment phase continues until the patient is withdrawn from Sym004 (As of Amendment 3)</p>
5.5 Number of Patients	<i>Not applicable</i>	*As of Amendment 3: Accrual to this trial has stopped and the total planned number of patients will not be enrolled.
6.3 Withdrawal from Trial Treatment	<i>Not applicable</i>	As of Amendment 3: The visit schedule for the treatment period will apply until

SECTION	ORIGINAL TEXT	NEW TEXT
		Sym004 has been discontinued. An EOT Visit will be performed within 10 days from the decision to withdraw treatment with Sym004, and a follow-up visit will be performed 1 month after the last administration of Sym004.
8.2.9.2 Biochemistry Panel	To include sodium, potassium, chloride...	To include, if applicable, sodium, potassium, chloride...
8.4 Pharmacokinetic Assessments (Dose-Escalation Only) 8.5 Anti-Drug Antibody Testing 8.6 Biomarker Tumor, Blood and Urine Sample (inclusive of 8.6.1 through 8.6.3)	<i>Entire section text</i>	<i>Sections are omitted as of Amendment 3</i>
9.1.1 Adverse Event	Please Note: Progression of disease will be captured as an AE.	Please Note: Progression of disease will not be captured as an AE/SAE unless the nature of the PD is different than expected (i.e. other diagnoses and/or signs/symptoms that are not typical of PD).
10.4.3 Pharmacokinetic Endpoint and Analyses 10.4.4 Pharmacodynamics Endpoints and Analyses	<i>Entire section text</i>	<i>Sections are omitted as of Amendment 3</i>
10.6 Data Collection and Analysis beyond Primary Analysis	<i>Not applicable</i>	As of Amendment 3: After the trial has closed enrollment and all DLT evaluation is completed, Sponsor may reduce trial data collection to information needed for safety reporting required by the FDA and/or other regulatory authorities, as well as efficacy and safety follow-up data considered necessary by the Sponsor.