Clinical Trial Protocol

Clinical Trial Protocol Number	EMR200637-002 (also designated Sym004-05)
Title	Open-label, Randomized, Controlled, Multicenter Phase II Trial Investigating 2 Sym004 Doses versus Investigator`s Choice (Best Supportive Care, Capecitabine, 5-FU) in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies
Trial Phase	II
IND Number	105953 (previously 119883)
EudraCT Number	2013-003829-29
Coordinating Investigator	Josep Tabernero, MD PhD Head, Medical Oncology Department Vall d'Hebron University Hospital Vall d'Hebron Institute of Oncology (VHIO) P. Vall d'Hebron 119-129 08035 Barcelona SPAIN Tel +34 93 489 4301 Fax +34 93 274 6059 jtabernero@vhio.net
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Sponsor's Legal Representative (EU)	Symphogen A/S, Pederstrupvej 93, 2750 Ballerup, Denmark
Clinical Trial Protocol Version	25 October 2016 / Version 5.0

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

See attached electronic signature and date

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I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Signature	Date of Signature

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Principal Investigator Signature

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Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature Date of Signature

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List of Abbreviations

ADA	Antidrug antibody
ADL	Activities of Daily Living
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BSC	Best supportive care
CRC	Colorectal cancer
CL	Clearance
C_{max}	Maximum concentration
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
DP	Drug product
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EU	European Union
FDA	Food and Drug Administration
5-FU	Fluorouracil (systemic)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
IWRS	Interactive web response system
mAbs	Monoclonal antibodies
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSAIDs	Nonsteroidal anti-inflammatory drugs

OR	Overall response
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
q1w	Every week
q2w	Every 2 weeks
q3w	Every 3 weeks
q6w	Every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of head and neck
SD	Stable disease
SUSARs	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
$t_{1/2}$	Half-life time
TdP	Torsades des pointes
t_{max}	Time of maximum plasma concentration
VD	Volume of distribution

1 Synopsis

Trial title	Open-label, Randomized, Controlled, Multicenter Phase II Trial Investigating 2 Sym004 Doses versus Investigator`s Choice (Best Supportive Care, Capecitabine, 5-FU) in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies
Trial number	EMR200637-002 (also designated Sym004-05)
EudraCT number	2013-003829-29
Sponsor	Symphogen A/S, Pederstrupvej 93, 2750 Ballerup, Denmark
Phase	II
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial center(s)/country(ies)	This study will be conducted at approximately 80 sites in 10 countries in Europe and North America.
Planned trial period **(first enrollment-minimum survival follow-up)**	February 2014 – October 2016
Trial objectives	**Primary:** The primary objective of this trial is to assess the efficacy of 2 different weekly dosing regimens (9 mg/kg loading dose followed by 6 mg/kg/week dose versus 12 mg/kg/week) of Sym004 compared with investigator's choice in terms of overall survival time in subjects with metastatic colorectal cancer (mCRC). **Secondary:** The secondary objectives of this trial are • To assess the efficacy of the 2 different weekly dosing regimens of Sym004 in subjects with mCRC in terms of best overall response and progression-free survival time and time to treatment failure; • To determine the safety profile of the 2 different weekly dosing regimens; • To evaluate the dose intensity until progression for the 2 different weekly dosing regimens; • To determine the pharmacokinetic (PK) profile;

	• To evaluate the occurrence of antidrug antibody (ADA); • To identify potential predictive biomarkers of response to treatment in blood and tumor tissue; • To evaluate quality of life.
Trial design and plan	This is a phase II, open-label, 3-arm trial randomized in the ratio of 1:1:1 to 2 Sym004 doses (Arms A and B) and a control group (Arm C) in subjects with mCRC and acquired resistance to anti-EGFR monoclonal antibodies (mAbs).
Planned number of subjects	240 subjects
Schedule of visits and assessments	Screening: • Informed consent, review of inclusion and exclusion criteria • Demographics, relevant medical history, concomitant medication • Documentation of prior cancer treatment • Tumor histology, mutation status, location and extent of disease • Safety laboratory assessments (hematology, coagulation, serum chemistry, pregnancy test) • Baseline safety assessments (symptoms and persisting toxicities from prior therapy to check compliance with inclusion criteria) • Serology testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) • Tumor assessment (baseline imaging) • Physical examination including vital signs, weight, height, dermatological examination, and ethnicity- • Eastern Cooperative Oncology Group (ECOG) performance status • 12-lead electrocardiogram (ECG) If all eligibility criteria are met and screening procedures are completed: • Voluntary tumor biopsy for biomarker evaluation (selected centers will include this as a mandatory biopsy)

	• Blood sampling for biomarker evaluation Treatment Phase: • Interactive web response system (IWRS) randomization within 2 weeks of screening (+ 1-2 weeks in case of medical issues or if biopsy taken) • First treatment dose within 72 hours of randomization • Physical examination • Vital signs • Dermatological examination • 12-lead ECG • ECOG performance status (PS) • Local laboratory tests (hematology, coagulation, and serum chemistry) • Pregnancy test (urine) • PK sampling • ADA sampling • Tumor assessment (computed tomography [CT] / magnetic resonance imaging [MRI]) • Adverse events (AEs) assessments • Concomitant medications • Quality of life questionnaires End of Treatment Visit To be performed when all treatments are discontinued, within 5 days after last treatment stopped: • Physical examination including weight and vital signs • ECOG PS • 12-lead ECG • Tumor assessment • Safety laboratory assessments (hematology, biochemistry, coagulation) • Pregnancy test (urine) • PK sampling

	• ADA sampling • AEs • Concomitant medications/procedures. End of Trial Intervention Visit: After assessment of PD, but no earlier than 28 days after treatment discontinuation. To be performed also for a subjects stopping trial intervention for reasons other than PD. • Physical examination including vital signs • AEs • Concomitant medication End of Trial Visit After end of trial intervention, all subjects will be followed for disease progression, subsequent anti-cancer treatment and survival until death, withdrawal of consent, loss-to-follow up or termination of whole trial.
Diagnosis and main inclusion and exclusion criteria	The primary inclusion criteria include the following: • Written informed consent obtained before undergoing any study-related activities • Male or female, at least 18 years of age • Subjects with histologically or cytologically confirmed mCRC, KRAS WT at initial diagnosis • Failure of or intolerance to all of the following – 5-FU – Oxaliplatin – Irinotecan • Acquired resistance to marketed anti-EGFR mAbs – Response while on previous treatment with marketed anti-EGFR mAb, defined as o Partial response (PR) or complete response (CR) and/or o Stable disease (SD) for more than 16 weeks – Documented progressive disease (PD) during or within 6 calendar months after cessation of previous anti-EGFR mAb treatment

	– No more than 6 calendar months from last dose of previous anti-EGFR mAb to randomization • Measurable disease defined as one or more target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) • Life expectancy of at least 3 months • ECOG performance status ≤ 1 The primary exclusion criteria include the following: • Pretreatment with regorafenib. • Subjects who in the opinion of the subject and investigator would benefit more from regorafenib treatment (except where regorafenib is not reimbursed in the country) • Skin rash Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1 from previous anti-EGFR therapy at time of randomization • Magnesium < 0.9 mg/dL • Known hypersensitivity to any of the treatment ingredients. Known previous Grade 3-4 infusion related reactions with anti-EGFR mAbs Note: Previous treatment with Avastin and/or Zaltrap is allowed, but not mandatory.
Investigational Medicinal Products: dose/mode of administration/ dosing schedule	Sym004 is an antibody mixture of 2 chimeric monoclonal antibodies against EGFR. Sym004 drug product (DP) is a 5.0 mg/mL solution presented in clear glass vials (Type 1) with a nominal fill volume of 30 mL. A subject will receive Sym004 administration weekly 12 mg/kg (Arm A) or weekly 9 mg/kg (loading) and followed by 6 mg/kg (Arm B) by intravenous (IV) infusion from Week 1 until unacceptable toxicity, disease progression, or consent withdrawal occurs, or until the subject meets any of the criteria for treatment or trial discontinuation. 5-FU and capecitabine will be administered in line with the local label; treatment may continue until disease progression.

Reference therapy(ies): dose/mode of administration/dosing schedule	Subjects assigned to Arm C will receive investigator's choice: best supportive care (BSC), or 5-FU, or capecitabine, per local standard of care.
Planned treatment duration per subject	The subject will receive weekly Sym004 administration by IV infusion from Week 1 until unacceptable toxicity, disease progression, or consent withdrawal occurs, or until the subject meets any of the criteria for treatment or trial discontinuation. Therefore, the duration of treatment will differ among individuals and cannot be fixed in advance.
Primary endpoint(s)	The primary endpoint is overall survival.
Secondary endpoint(s)	The secondary endpoints are as follows: • Best overall response according to RECIST v1.1 • Progression-free survival time • Time to treatment failure • Occurrence and nature of AEs • Discontinuation due to AEs • Relative dose intensity • PK profile • Host immune response: ADA • Biomarkers: including but not limited to RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels • Quality of life
Pharmacokinetics	Based on the concentrations determined, the following PK parameters for Sym004 will be calculated for each subject: area under concentration-time curve (AUC) from start of first infusion to 168 hours (AUC_{0-168}), half-life ($t_{1/2}$), clearance (CL), volume of distribution (VD), maximum concentration (C_{max}), trough concentration (C_{trough}), and time to reach C_{max} (t_{max}).
Statistical methods (includes sample size calculation)	This is an open label, randomized, 3-arm trial where the subjects will be randomized in the ratio of 1:1:1 to 2 Sym004 doses (Arms A and B) and a control group (Arm C). Median overall survival time is expected to be 6 months in the control

	arm and 9.2 months in each of the Sym004 arms, i.e., a hazard ratio (HR) of 0.65. A total number of 181 events (67 in the control arm and 57 in each Sym004 arm) will give 80% power for each Sym004 arm to detect the assumed difference to the control arm in overall survival time with a 20% two-sided overall significance level, using a multiple comparison procedure developed by Dunnett. Using Schoenfeld's formula, the per-comparison significance level of 0.121 would correspond to a critical value of an observed HR of 0.756. A total number of 240 subjects (assuming a drop-out rate of 5%), recruited in 22 months, is expected to yield 181 events after a follow-up time of 9 months.

2 Sponsor, Investigators, and Trial Administrative Structure

The sponsor of this clinical trial with Sym004 is Symphogen A/S, Pederstrupvej 93, 2750 Ballerup, Denmark.

Details of logistic and administrative structures and associated procedures for execution of the trial will be defined in a separate study specifications document. This will be prepared under the supervision of the Clinical Trial Leader in close collaboration with the responsible units of the sponsor.

2.1 Investigational Sites

The trial will be conducted at approximately 80 sites in 10 countries in Europe and North America. The participating sites will be confirmed at the time of selection. A few selected sites will subscribe to the mandatory tumor biopsy study.

2.1.1 Key Parties

The clinical conduct of this trial will be overseen by Quintiles, a contract research organization (CRO). The key parties involved in the conduct of the trial are listed in Table 2-1.

Table 2-1 Trial Administrative Structure

Project Management: Quintiles Europe Quintiles Inc., USA	**Manufacture of Drug Product:** Patheon UK Ltd, Swindon, UK
Trial Monitoring: Quintiles Europe Quintiles Inc, USA	**Trial Drug Packaging and Labeling:** Catalent Pharma Solutions Bathgate, Scotland, UK Kansas City, USA
Drug Safety Reporting: Quintiles Ireland Ltd, Dublin, Ireland	**Biomarker Analyses:** Guardant Health, Inc. Redwood City, CA, USA Myriad RBM, Inc. Austin, TX, USA
Biostatistics: Quintiles UK Ltd, Reading, UK	**Pharmacokinetic/Immunogenicity Analyses** Covance, Inc., Harrogate, UK
Data Management: Quintiles Strasbourg, France	

2.2 Trial Coordination/Monitoring

The sponsor will coordinate the trial and will subcontract to the CRO, Quintiles, for the management of most of the activities of the trial, as well as for providing support services for the centralized activities.

The sponsor will supply Sym004 to the sites. Safety laboratory assessments will be performed locally by trial sites. Pharmacokinetics (PK), gene expression profiling, and biomarker analyses will be performed centrally under the responsibility of the sponsor.

The sponsor's Global Drug Safety Department or its designated representative will supervise all drug safety activities and the timely reporting of adverse events (AEs) and serious adverse events (SAEs). Safety reporting to Health Authorities, according to local regulatory requirements, will be the responsibility of the sponsor or its designated representatives.

Monitoring and data management will be performed by Quintiles, and the sponsor or designee will be responsible for regulatory submission. Quality assurance of the trial conduct will be performed by the sponsor's Development Quality Assurance. Quintiles will write the trial statistical analysis plan (SAP), perform the statistical analyses, and will provide the outputs from the statistical analyses.

2.2.1 Data Monitoring Committee

In order to ensure ongoing regular safety monitoring, an independent data monitoring committee (DMC) will be established to review all relevant safety and toxicity data of available subjects on a regular basis.

The first DMC meetings will take place after 6 and after 12 subjects in each experimental arm (Arm A Sym004 at 12 mg/kg/week, Arm B Sym004 at 9 mg/kg loading followed by 6 mg/kg/week maintenance) have completed at least one cycle of treatment (defined as 3 weeks). During the data review, the enrollment of further subjects will be suspended. The DMC will review all emergent safety data and will evaluate whether there is any evidence for excess of toxicity compared to data derived from previous trials Sym004-01 and Sym004-02. The DMC will provide a recommendation on whether to continue the trial unchanged, continue with changes (which might include extension of the monitoring period, further DMC meetings, discontinuation of one dose, exploration of a lower dose) or discontinue. No further patients will receive the investigational product until the recommendation of the DMC will be issued and processed.

This safety monitoring will be performed on the monitored but not fully cleaned data. Further details will be described in the DMC charter. No interim analysis on efficacy data is planned to be performed.

3 Background Information

3.1 Target Patient Population

In 2008, the worldwide incidence of colorectal cancer (CRC) in both sexes was estimated to be over 1.2 million (1). The risk of developing CRC increases with age. Adults, who are aged 50 or older, have inflammatory bowel disease, are overweight or physically inactive, and those who have a personal or family history of colorectal polyps or CRC are at higher risk.

Approximately 15% to 25% of patients with CRC will have hepatic metastases at the time of clinical presentation (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). Survival for stage I is 85% to > 90%, while 5-year survival for Stage II is 70% to 80%. For Stage III disease, 5-year survival is significantly lower, in the order of 25% to 60%. Eventually, 50% of all patients with CRC will relapse and die due to metastatic disease within 5 years after being diagnosed with CRC. Metastatic CRC (mCRC) is treated with different regimens of combination chemotherapy and targeted agents including anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs). Late stage mCRC (after failure of the available standard therapies) remains an indication of very high unmet need.

3.2 Description of Sym004

The name of the IMP investigated in this trial is Sym004. Sym004 is a mixture of 2 mouse-human chimeric immunoglobulin G1 EGFR antibodies (called 992 mAb and 1024 mAb). Each monoclonal antibody is manufactured by Chinese hamster ovary cells, transfected with an expression vector coding for both the antibody light chains and heavy chains. Each antibody is manufactured individually as a drug substance (992 DS and 1024 DS, respectively) and the Sym004 drug product (DP) is prepared as a 1:1 ratio mixture of these 2 drug substances. The DP contains 150 mg of active substances in 30 mL vials closed with rubber stopper and cap.

3.3 Mechanism of Action of Sym004

EGFR has proven to be a clinically meaningful target in colorectal cancer. Efficacy has been established for anti-EGFR mAbs (cetuximab , panitumumab) in all lines of treatment of mCRC and in combination with different chemotherapy regimens. Both cetuximab and panitumumab are approved drugs for the treatment of metastatic colorectal cancer. However, there are nonresponders to these agents and patients will ultimately develop resistance to anti-EGFR mAbs.

Sym004 consists of 2 anti-EGFR antibodies that bind to 2 nonoverlapping epitopes on domain III of the EGFR. The binding of both antibodies 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 then degradation of the internalized receptor protein that leads to down-regulation of EGFR and subsequent inhibition of cancer cell growth. There is considerable in vitro and in vivo evidence that suggests Sym004 to be superior to existing anti-EGFR antibodies of cetuximab and panitumumab in a wide range of cancer types. Furthermore, Sym004 has shown activities also in cancer cells with acquired resistance to cetuximab (3).

3.4 Summary of Nonclinical Findings

The nonclinical safety profile of Sym004 was investigated in cynomolgus monkeys and included a comparison with an approved anti-EGFR antibody (cetuximab) and a safety assessment of the two individual antibodies, 992 mAb and 1024 mAb.

The increased potency and pharmacological activity of Sym004 demonstrated in vitro and in vivo did not translate into a distinct safety profile in monkeys, but induced an accelerated onset of expected anti-EGFR mediated pharmacological effects. This was shown in the nonpivotal main dose range finding study, where the toxicity profile of Sym004 was compared with cetuximab at

24/16 mg/kg (loading dose/maintenance dose). In this study, skin rash was noted in all animals at all dose levels, starting from 12/8 mg/kg, and a no-observed-adverse-effect-level (NOAEL) was not found. Therefore, Sym004 DP was tested at 2, 7, and 14 mg/kg/week in the pivotal repeat dose toxicity study, in which monkeys received a total of 8 weekly intravenous administrations. A loading dose regimen was not used in this study.

Weekly dosing for 8 weeks of 14 mg/kg Sym004 resulted in expected clinical observations such as treatment-requiring skin rash, liquid feces, and dehydration. These findings were much less severe and less frequent after dosing with 7 mg/kg and absent after dosing with 2 mg/kg. Sym004 showed a good local tolerance in monkeys and no cardiovascular effects were observed after intravenous (IV) doses of Sym004 up to 14 mg/kg. The individual antibodies did not elicit any or only very mild treatment-related effects. No clear gender differences were noted for any parameter investigated and all clinical observations, except a single case of rash, showed reversibility during the recovery period (4 weeks).

Based on the range and incidence of findings in the 14 mg/kg group, and the minimal effects observed at 7 mg/kg/dose, the level of 7 mg/kg Sym004 is considered to be the NOAEL in the pivotal repeat dose toxicity study.

Tissue cross reactivity studies showed that Sym004 bound to panels of tissues from human and cynomolgus monkeys with similar distribution patterns, frequency, and intensity; thus, supporting the use of cynomolgus monkeys in the animal toxicity studies.

For the details on nonclinical findings, please see the relevant sections of the latest Investigator's Brochure of Sym004 (version 1.0 dated 19 September 2013).

3.5 Summary of Clinical Findings

Two trials have been conducted in subjects with recurrent advanced solid tumors: Sym004-01 (ongoing) and Sym004-02; to date (data cut-off 20 Jan 2013), 97 subjects had been exposed to Sym004.

Study Sym004-01, "An open-label, multi-center, phase I, dose escalation study to investigate the safety and tolerability of multiple doses of Sym004 in patients with advanced solid tumor", was comprised of Part A (investigating the safety and PK of escalating doses of Sym004 in subjects with recurrent advanced solid tumors), and Parts B through F (validating the safety and PK and exploring efficacy of various Sym004 doses in subjects with mCRC and acquired resistance to anti-EGFR mAbs). Subjects in Part B and Part C were treated at weekly doses of 12 and 9 mg/kg respectively, and subjects in Part D and Part E received doses of 12 and 18 mg/kg every second week (biweekly). Subjects in Part F received a loading dose of 9 mg/kg and weekly doses of 6 mg/kg thereafter. Study Sym004-02 was an open-label, single arm, phase 2 trial to investigate the safety and efficacy of Sym004 in subjects with recurrent and/or metastatic squamous cell carcinoma of head and neck (SCCHN) who had failed anti-EGFR mAb-based therapy. All enrolled subjects received weekly infusions of 12 mg/kg Sym004.

Preliminary data on trial Sym004-01 were presented at ASCO 2013: 42 patients were enrolled at 9 mg/kg/week (n=13) and 12 mg/kg/week (n=29). Tumor shrinkage of more than 10% was

documented in 4/12 (33%) subjects at 9 mg/kg, with partial response (PR) in 1/12 (8%) subjects. At 12 mg/kg, 7/27 (26%) subjects had more than 10% tumor shrinkage, with PR in 3/27 (11%) subjects. Median progression-free survival was 13.6 weeks (95% CI: 5.3-23) and 13.7 weeks (95% CI: 5.9-18.6), respectively. Similar response rates are reported for cetuximab in the same treatment line, but in subjects naïve to anti-EGFR mAbs (4). Efficacy data on further dose levels are pending.

The most frequently reported AEs in the Sym004-01 and Sym004-02 trials were similar to the most common events associated with other anti-EGFR mAbs, such as skin toxicities (acne and rash, pruritus, skin fissures, dry skin and erythema), electrolyte disturbances (particularly hypomagnesemia), mucosal inflammation, diarrhea and nausea, albeit more subjects experienced Grade 3 skin reactions and Grade 3/4 hypomagnesemia. Infusion reactions have also been reported. Skin toxicities were seen in 80% to 97% of subjects; 50% to 69% of subjects receiving 9 or 12 mg/kg weekly (Sym004-01 Parts B and C and Sym004-02) experienced Grade 3 skin toxicities, but no Grade 4 toxicities were seen. Hypomagnesemia was reported in 30% to 65% of subjects; up to 38% of subjects experienced Grade 3/4 hypomagnesemia. Mucosal inflammation and diarrhea have been reported in around 25% of subjects each; all these events were of Grade 1-2 except one case of Grade 3 diarrhea. Other Grade 3 and 4 events included fatigue, sepsis, and anemia.

The adverse reactions were manageable and resolved with continued therapy although in some cases, skin rash required temporary or permanent interruption of therapy before improvement occurred.

A total of 112 SAEs were reported in 64 of the 97 subjects; 20 of these were evaluated as related to trial drug, the most common of which were hypomagnesemia and rash. Forty-two SAEs with fatal outcome have been reported. Two of these were evaluated as related to trial drug.

For the details on clinical findings and updated safety data, please see the relevant sections of the latest investigator's brochure of Sym004.

3.6 Trial Rationale

Although the use of anti-EGFR mAbs is well established in the setting of advanced mCRC and SCCHN, there is still a proportion of patients with advanced disease who become resistant to chemotherapy and anti-EGFR therapy. These patients have limited treatment options. The distinct mechanism of action of Sym004 compared with available anti-EGFR mAbs, and the promising data provided by nonclinical tests, indicate that it may provide highly effective antitumor activity in clinical resistant settings.

Following treatment with EGFR inhibitors, such as cetuximab and panitumumab, tumors may develop resistance to the treatment by a variety of factors. One common mechanism of resistance is based on increased production of ligands (5). Sym004 may be able to overcome this resistance mechanism by a more pronounced down regulation of the expression of EGFR. Such hypothesis is supported by the demonstration of clinical activity in subjects considered to be resistant to anti-EGFR mAbs with an observed response rate in a range otherwise expected for cetuximab and panitumumab in an anti-EGFR mAb naïve setting.

First clinical data in subjects with mCRC and acquired resistance to anti-EGFR mAbs show activity for Sym004 in this advanced stage cancer population. Response rates of 10% and tumor shrinkage (of ⩾ 10%) in approximately 30% of subjects at doses of 9 mg/kg/week (n = 13) and 12 mg/kg/week (n = 29) were observed in and reported at ASCO 2013 (6).

The more effective EGFR inhibition by Sym004 is associated with a more pronounced safety profile as compared to the labeled anti-EGFR mAbs. In summary, the overall pattern of the observed adverse events appears similar, however more severe. Grade 3 rash has been reported in ~ 50% of all patients and Grade 3/4 (asymptomatic) hypomagnesemia in ~ 30% of subjects (refer to Section 3.5 for details). Rash was a frequent cause for dose omissions and reductions. No clear difference was seen between the two dose levels tested.

Based on the above mentioned data, this randomized phase II trial aims at demonstrating proof-of-concept in subjects with mCRC and acquired resistance to anti-EGFR mAbs. Two different doses will be explored to allow selection of the dose/regimen resulting in the optimal benefit/risk ratio (rationale for dose selection, please refer to Section 5.2 “discussion of trial design”).

3.7 Summary of Overall Benefit and Risk

As previously discussed, preclinical data in addition to preliminary clinical data in subjects with mCRC and acquired resistance to anti-EGFR mAbs have shown activity for Sym004 in this advanced stage cancer population. Response rates of 10% and tumor shrinkage (of ⩾ 10%) in ~ 30% of subjects at doses of 9 mg/kg/week (n = 13) and 12 mg/kg/week (n = 29) were observed.

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

Based on this clinical experience, more effective mitigation strategies to prevent skin toxicities and a lower dose of Sym004 will be evaluated in this trial. The following doses will be explored concomitantly with prophylactic measures:

- 12 mg/kg/week
- 9 mg/kg loading, followed by 6 mg/kg/week

Prophylactic and reactive treatment guidelines for skin management are being implemented into this trial to reduce the incidence of severe rash (refer to Section 6.4 “Prophylactic and Reactive Treatment of Sym004-induced Skin Toxicities”). Based on data derived from randomized controlled trials using this approach, e.g., skin toxicity evaluation protocol with panitumumab (STEPP) trial (7), it is anticipated, that the incidence of Grade 3 rash will be reduced by these measures.

Given the setting of unmet need for alternative treatments for mCRC and what is currently known about the safety profile for Sym004, the risk-benefit relationship has been carefully considered in the planning of the trial. Based on the preclinical and clinical data available to date, the conduct of the trial is considered justifiable with using the doses and dosage regimens of the IMP as specified in this clinical trial protocol. In this trial, as applicable, a DMC is planned for the ongoing

assessment of the risk-benefit ratio. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (International Council for Harmonisation [ICH] Topic E6, GCP) and the applicable regulatory requirements.

4 Trial Objectives

4.1 Primary objective

The primary objective of this trial is to assess the efficacy of 2 different weekly dosing regimens (9 mg/kg loading dose followed by 6 mg/kg/week dose versus 12 mg/kg/week) of Sym004 compared with investigator's choice in terms of overall survival time in subjects with mCRC.

4.2 Secondary objectives

The secondary objectives of this trial are

- To assess the efficacy of the 2 different weekly dosing regimens of Sym004 in subjects with mCRC in terms of best overall response and progression-free survival time and time to treatment failure;
- To determine the safety profile of the 2 different weekly dosing regimens;
- To evaluate the dose intensity for the 2 different weekly dosing regimens;
- To determine the PK profile, area under concentration-time curve to 168 hours ($AUC_{0\text{-}168h}$), time to reach maximum concentration (t_{max}), half-life time ($t_{1/2}$), clearance (CL), volume of distribution (VD), maximum concentration (C_{max}), and trough concentration (C_{trough});
- To evaluate the occurrence of antidrug antibody (ADA);
- To identify potential predictive biomarkers of response to treatment including but not limited to RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands [e.g., amphiregulin, TGF-α, heregulin] plasma protein levels; tumor localization;
- To evaluate quality of life by subject reporting questionnaires including EORTC QLQ-C30 (version 3), EORTC QLQ-CR29 and FACT-EGFR18 for skin rash.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a phase II, open-label, 3-arm trial randomized in the ratio of 1:1:1 to 2 Sym004 doses (Arms A and B) and a control group (Arm C) in subjects with mCRC and acquired resistance to anti-EGFR mAbs. Safety, clinical, and biological endpoints will be included in this trial, including overall survival (OS), best overall response (OR), progression-free survival (PFS), time to treatment failure, AEs, discontinuations of treatment due to AEs, relative dose intensity, PK,

ADAs, biomarkers, and quality of life. A total number of 240 subjects (assuming a drop-out rate of 5%), recruited in 22 months, is expected to yield 181 events after a follow-up time of 9 months. A data monitoring committee will be established to review all relevant safety and toxicity data of available subjects on a regular basis. Sym004 dose reductions will occur for those subjects experiencing Grade 3 skin toxicities per the guidelines in Section 6.2.4.

Trial Treatment

The trial treatment will consist of single-agent Sym004 or investigator's choice: BSC, 5-FU or capecitabine, as follows:

- Arm A: Sym004 single agent, 12 mg/kg/week, IV infusion
- Arm B: Sym004 single agent, 9 mg/kg loading, thereafter 6 mg/kg/week, IV infusion
- Arm C: Investigator's choice: BSC, 5-FU or capecitabine

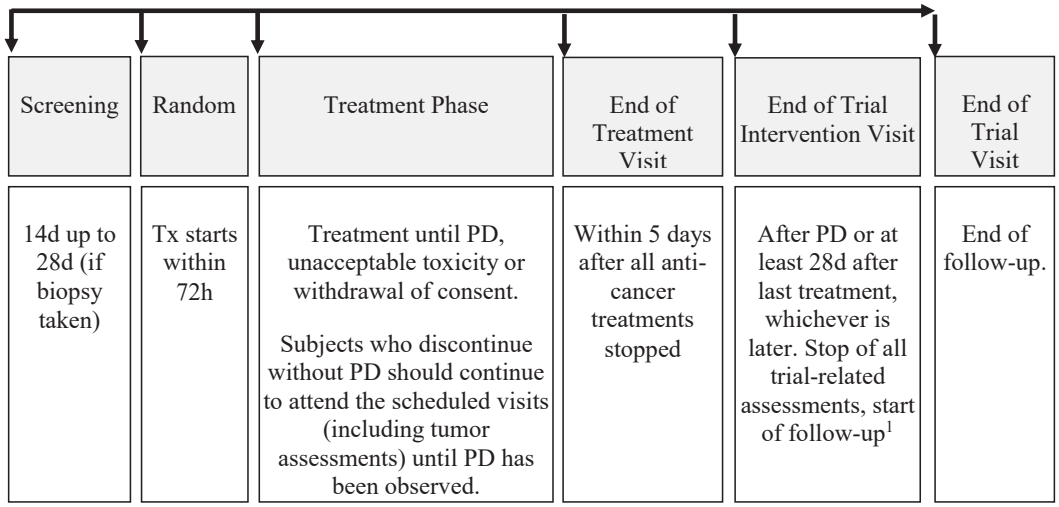
Sym004 will be administered at different IV doses every week (q1w) (± 2 days) according to the allocated Arm at randomization. Administration of 5-FU and capecitabine will be given at doses and schedules at the investigators' discretion and in line with the local package insert. BSC is the best palliative care per investigator excluding antineoplastic agents. BSC may include, but is not limited to, antibiotics, analgesics, antiemetics, blood transfusions and nutritional support.

Study Periods/Visits

The trial will consist of the following periods/visits (see Figure 5.1):

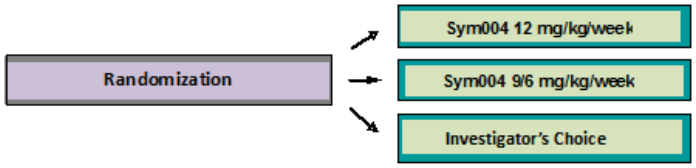
- Screening (Day -28 to -1)
- Treatment Phase (Day 1 to progressive disease, excessive toxicity or withdrawal of consent)
- End-of-treatment Visit (within 5 days after discontinuation of all study treatment)
- End of Trial Intervention Visit (after assessment of PD, but no earlier than 28 days after treatment discontinuation, to be performed also for subjects stopping trial intervention for reasons other than PD)
- End of Trial Visit (follow up every 6 weeks for disease progression (if not assessed before), subsequent anti-cancer treatment and survival until death, withdrawal of consent, lost-to-follow up or termination of whole trial.

Figure 5.1 **Study Periods/Visits**



[1]For subjects with PD: Follow up for survival and subsequent anti-cancer treatment every 6 weeks. For subjects without PD (e.g., withdrawal of consent): Follow-up for disease progression, survival and subsequent anti-cancer treatment every 6 weeks.

Figure 5.2 **Treatment Allocation**



Endpoints

Study endpoints are described in Section 8.3.

Termination of Treatment

The foreseen treatment duration is until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from treatment and/or the trial or IMP occurs.

The investigator may perform imaging in addition to a scheduled trial assessment for medical reasons or if the investigator suspects PD. Scheduled tumor assessments are to be continued until PD in case treatment is stopped prior to PD.

5.2 Discussion of Trial Design

This is a phase II, open-label, randomized, 3-arm trial, where the subjects will be randomized in the ratio of 1:1:1 to two Sym004 doses (Arms A and B) and a control group (Arm C). This trial is not a blinded trial as the incidence of rash (approximately 95%) for Sym004 does not allow true blinding.

The choice of Group C treatments, BSC, or capecitabine, or infusional 5-FU will allow investigators using control arm treatments that are considered to provide some benefit in a late line setting with a very well-known and manageable side effect profile. Recently a median overall survival of 6.8 months has been reported for capecitabine in the same treatment line (8). Doses and regimens for 5-FU and capecitabine are at the investigator's discretion. Only regorafenib-naïve subjects will be eligible for this trial because of the very short life expectancy after failure of regorafenib and severe regorafenib-induced fatigue and hand-foot syndrome may negatively impact eligibility for and outcome of subsequent treatments.

As previously discussed, the choice of Sym004 dose levels was intended to provide on the one hand the highest efficacious dose that would not result in unacceptable incidence of severe rash, and on the other hand, a dose that is sufficiently lower to allow detection of any potential differences in efficacy and safety but which is still high enough to offer a reasonable expectation of clinical benefit. The following doses will be explored concomitantly with prophylactic measures:

- 12 mg/kg/week
- 9 mg/kg loading dose, followed by 6 mg/kg/week

The "9/6" dose is sufficiently lower than 12 mg/kg/week to allow detection of differences in efficacy/safety, if present. No lower dose than 6 mg/kg/week is being explored based on available clinical data (only sporadic tumor shrinkages below 6 mg/kg/week in phase I) and PK/pharmacodynamic modeling (similar level of target occupancy to cetuximab expected at dose levels ranging from 6 to 12 mg/kg/week). A loading dose of 9 mg/kg will reduce the time to steady state.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

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

1. Written informed consent obtained before undergoing any study-related activities
2. Male or female, at least 18 years of age
3. Subjects with histologically or cytologically confirmed mCRC, *KRAS* WT at initial diagnosis
4. Failure of or intolerance to all of the following
    a. 5-FU
    b. Oxaliplatin
    c. Irinotecan
5. "Acquired resistance" to marketed anti-EGFR mAbs
    a. Response while on previous treatment with marketed anti-EGFR mAb, defined as
        i. Partial response (PR) or complete response (CR) and/or
        ii. Stable disease (SD) for more than 16 weeks
    b. Documented PD during or within 6 calendar months after cessation of previous anti-EGFR mAb treatment
    c. No more than 6 calendar months from last dose of previous anti-EGFR mAb to randomization
6. Measurable disease defined as one or more target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST)
7. Life expectancy of at least 3 months
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
9. Women of childbearing potential must have a negative blood pregnancy test at the screening visit. For this trial, women of childbearing potential are defined as all women after puberty, unless they are postmenopausal for at least 12 months, are surgically sterile, or are sexually inactive
10. Subjects and their partners must be willing to avoid pregnancy during the trial and until 6 months after the last trial treatment. Male subjects with female partners of childbearing potential and female subjects of childbearing potential must, therefore, be willing to use adequate contraception as approved by the investigator, such as a two-barrier method or one-barrier method with spermicidal or intrauterine device. This requirement begins two

weeks before receiving the first trial treatment and ends 6 months after receiving the last treatment.

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Intake of any investigational drug or any anticancer therapy in the 30 days (or 5 half-lives for noncytotoxics, whichever is shorter) before start of trial treatment
2. Pretreatment with regorafenib.
3. Subjects who in the opinion of the subject and investigator would benefit more from regorafenib treatment (except where regorafenib is not reimbursed in the country)
4. Diarrhea Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1
5. Skin rash CTCAE Grade > 1 from previous anti-EGFR therapy at time of randomization
6. Magnesium < 0.9 mg/dL
7. Abnormal organ or bone marrow function defined as
    a. absolute neutrophil count < 1.5 x 10^9/L
    b. hemoglobin < 9 g/dL
    c. platelet count < 75 x 10^9/L
    d. alkaline phosphatase > 2.5 x upper normal limit (ULN)
    e. aspartate aminotransferase AST/ alanine aminotransferase (ALT) > 2.5 x ULN
    f. bilirubin > 1.5 x ULN
    g. serum creatinine > 1.5 x ULN and/or creatinine clearance ≤ 50 mL/min calculated according to Cockroft-Gault

    In case of metastatic liver disease:
    h. AST/ALT > 5 x ULN
    i. alkaline phosphatase > 5 x ULN
    j. bilirubin > 2 x ULN
8. Known brain or leptomeningeal metastasis
9. History of other malignancy within 5 years prior to trial start, with the exception of basal cell carcinoma of the skin and carcinoma in situ of the cervix
10. Significant disease which, in the investigator's opinion, would exclude the subject from the trial
11. Active infection (requiring IV antibiotics), including active tuberculosis, active (acute or chronic) Hepatitis B or C, or ongoing HIV infection
12. Known hypersensitivity to any of the treatment ingredients. Known previous Grade 3-4 infusion related reactions with anti-EGFR monoclonal antibodies
13. Clinically significant cardiovascular disease, e.g., cardiac failure of New York Heart Association classes III to IV, uncontrolled coronary artery disease (history of myocardial

infarction or instable angina pectoris in the last 12 months), cardiomyopathy, QT prolongation (marked baseline prolongation of QT/QTc interval, e.g., repeated demonstration of a QTc interval >450 ms) and history of ventricular cardiac arrhythmia including torsades des pointes (TdP), uncontrolled hypertension, or history of myocardial infarction in the last 12 months

14. Known drug abuse or alcohol abuse
15. Legal incapacity or limited legal capacity
16. Medical or psychological conditions that would not permit the subject to complete the trial or sign the informed consent
17. Pregnancy or lactation
18. Concurrent chronic immunosuppressive or hormone anticancer therapy (physiologic hormone replacement allowed)

Note: Previous treatment with Avastin and/or Zaltrap is allowed, but not mandatory.

5.4 Criteria for Randomization/Initiation of Treatment with the Investigational Medicinal Product

This is a randomized open-label trial. Investigators, other members of the site trial team, Sponsor personnel and subjects will be aware of the identity of the trial treatments.

Trial treatment will only be initiated for those subjects who fulfill all the inclusion criteria and do not meet any of the exclusion criteria as assessed at the Screening Visit 1 and prior to the first dose of IMP on Day 1 (Visit 1), where applicable.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn from treatment and trial intervention in the event of any of the following:

- Withdrawal of the subject's consent
- Participation in any other trial during the duration of this trial prior to the end of trial intervention visit
- Receipt of another non-study anti-cancer treatment prior to the end of trial intervention visit.

If a subject has failed to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, the assessments scheduled for the End of Trial Intervention Visit should be performed, if possible, with focus on the most relevant assessments

(see Section 7.1, Schedule of Assessments). The collection of survival and disease follow-up data should be performed (if consent is not withdrawn for collection of survival/disease follow-up data). In any case, the appropriate electronic case report form (eCRF) section must be completed.

5.5.2 Withdrawal from Sym004

The subject must be withdrawn from treatment with Sym004 in the event of any of the following:

- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the investigator and/or sponsor
- Occurrence of adverse events, if discontinuation of trial drug is desired or considered necessary by the Investigator and/or the subject
- Occurrence of pregnancy
- Use of a non-permitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP
- TDP arrhythmias or other life-threatening cardiac arrhythmias
- Infusion-related reaction of ≥ Grade 3 according to NCI-CTCAE (v4.03)
- Disease progression (verified by imaging technique and evaluated according to RECIST v1.1)
- EGFR-associated skin toxicity of Grade 4 according to NCI-CTCAE (v4.03)
- Diarrhea of Grade 4 according to NCI-CTCAE (v4.03)

Patients who discontinue study treatment prior to the assessment of PD should continue to attend scheduled study visits until PD has been confirmed.

In case of withdrawal from the IMP, the assessments scheduled for the End of Treatment assessment) should be performed. In any case, the appropriate eCRF section must be completed. Patients who discontinue study treatment should continue to attend scheduled study visits until PD has been confirmed.

5.6 Premature Discontinuation of the Trial

The whole trial may be terminated prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g., due to
    - evidence of inefficacy of the IMP,
    - occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
    - other unfavorable safety findings.

(Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g., toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the sponsor's IMP

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

5.7 Definition of End of Trial

The primary analysis milestone for the trial is defined as the time that at least 181 events (deaths) are reported or 12 months after the last subject was randomized in the trial, whichever occurs later. Additional survival follow-up, beyond the primary analysis milestone, will extend up to 2 years after the last patient is randomized in the trial. If subjects remain on treatment beyond 2 years, the end of the trial will be defined as 28 days after the last subject receives the last dose of trial treatment.

6 Investigational Medicinal Products and Other Drugs Used in the Trial

The term Investigational Medicinal Product refers to Sym004, capecitabine and 5-FU within this trial.

6.1 Description of Investigational Medicinal Products

Sym004 is an antibody mixture of 2 chimeric monoclonal antibodies against EGFR.

Sym004 DP is a 5.0 mg/mL solution presented in clear glass vials (Type 1) with a nominal fill volume of 30 mL. The closure system for the IMP vials consists of fluororesin-coated halobutyl/butyl rubber stoppers, secured with caps having flip-off seals. The materials used are of pharmacopeial quality and are considered suitable for storage of sterile injectable solutions. Sym004 will be filtered using an inline filter (0.2 μm) during infusion.

Oral capecitabine and 5-FU (fluorouracil injection USP) are marketed drugs that will be administered per the local package inserts as stated in the respective SmPC.

Table 6-1 Description of Sym004

Characteristic	Description
Product name	Sym004
Physical appearance	Clear to opalescent, colorless to slightly yellow solution
Dosage	Weekly
Dose per application	6 mg/kg, 9 mg/kg, 12 mg/kg
Route of administration	Intravenous infusion
Manufacturer	Patheon UK Ltd, UK

A sufficient quantity of vials containing Sym004 for the three dose levels will be supplied by the Sponsor, together with certificates of analysis, material safety data sheets, use by dates and a statement that the trial medication has been manufactured in accordance with Good Manufacturing Practice (GMP).

6.2 Dosage and Administration

6.2.1 Dosing Regimens

Sym004 will be administered at different weekly doses by IV infusion. The first administration of Sym004 will be performed on the same day as randomization or no later than 72 hours after randomization. Thereafter, Sym004 is administered q1w (±2 days).

Administration of Investigator's choice treatment will be according to the local approved product labeling.

The IMP infusions will take place under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available.

6.2.2 Handling and Preparation of the IMP

All handling and preparation of the IMP should take place at the pharmacy of each trial site. The investigator is responsible for informing the pharmacy of the dose of Sym004 administered to the subject with the subject's body weight. Every dose must be prepared according to the recent body weight value captured every 3 weeks following baseline.

Preparation of the infusion bag should be done immediately before the infusion start. The infusion must be completed within 8 hours after preparation. Sym004 will be diluted in saline prior to administration; the volume of saline will depend on the dose level: 500 mL for dose levels of 6 mg/kg or lower, 1000 mL for dose levels of 9 to 12 mg/kg.

6.2.3 Administration of the IMP

6.2.3.1 Sym004

Sym004 is administered by IV infusion through a peripheral line or indwelling catheter and with or without the use of an infusion pump. Sym004 will be filtered using an inline filter (0.2 µm) during infusion. For all infusions, the start and stop times, dose of Sym004, and total volume infused will be recorded in the eCRF to obtain a complete dosing history. To prevent and minimize infusion-related reaction of Sym004, mandated premedication has been set (see Section 6.2.4.3). Special care has also been taken for the infusion rate of Sym004, which is shown in Table 6-2.

For the first 4 infusions, the infusion rate should be increased every 30 minutes to a maximum of 700 mL/hour. Thus, a maximum of 10 mg Sym004 will be delivered per minute and per kg body weight.

Table 6-2 Infusion Rates of Sym004 Administration

Time	Dose 12 mg/kg		Dose 9 mg/kg		Dose 6 mg/kg	
min	ml/hr	mg/30min[a]	ml/hr	mg/30min[a]	ml/hr	mg/30min[a]
0-30	75	31.5	75	23.6	90	37.8
31-60	150	63	150	47.2	150	63.0
61-90	300	126	300	94.5	260	109.2
91-120	600	252	600	189	500	210.0
121-160	700	294	700	220	NA	NA

a Calculation based on a 70 kg person

After the fourth infusion, the infusion rates can be increased at the discretion of the investigator.

Previous infusion-related reactions and the volume of infusion (up to 1000 mL) must be taken into account when assessing whether it is safe to infuse Sym004 at higher rates for an individual subject.

The subject should be monitored for at least one hour post-infusion. 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

6.2.4 Dose Adjustment and Modification

An administrative dose of Sym004 is determined by the treatment arm and the subject's body weight in this trial. However, dose adjustments should be performed for obese subjects (see Section 6.2.4.1). Intra-subject dose reduction or temporal discontinuation of Sym004 will also be required upon occurrence of anti-EGFR-associated skin toxicity as specified (see Section 6.2.4.2).

6.2.4.1 Obese Subjects

If a subject's body mass index (BMI) exceeds 30, the dose is adjusted according to the below algorithm:

Adjusted dose (unit: mg) = 30 (unit: kg/m^2) x $height^2$ (unit: m^2) x planned dose (unit: mg/kg)

For example, if the planned dose is 12 mg/kg (unless dose is reduced due to skin toxicity) and the patient is obese with height of 1.62 m and weight of 90.0 kg, the dose without adjustment would have been:

12 mg/kg x 90.0 kg = 1080.0 mg

The adjusted dose according to the algorithm provided is:

Adjusted dose = 30 kg/m^2 x $(1.62\ m)^2$ x 12 mg/kg = 944.8 mg

6.2.4.2 Occurrence of anti-EGFR-associated Skin Toxicity

Dose modification guidelines on the occurrence of Grade 3 EGFR-associated skin toxicity according to NCI-CTCAE (v4.03) are summarized below.

Dose reduction in the Sym004 arms is to occur as outlined in Table 6-3.

Table 6-3 Sym004 Dose Reduction Rules

Arm A (12 mg/kg/week)				
Dose	**Occurrence**	**Recovery to grade**	**Dose Reduction to**	**Dose Level (DL)**
Delay treatment, re-assessment after 1-2 weeks[a]				
12 mg/kg/week	1st occurrence	0,1	No change	-
12 mg/kg/week	1st occurrence	2	9 mg/kg/week	-1
12 mg/kg/week	2nd occurrence	0,1,2	9 mg/kg/week	-1
9 mg/kg/week	2nd occurrence	0,1,2	6 mg/kg/week	-2
9 mg/kg/week	3rd occurrence	0,1,2	6 mg/kg/week	-2
6 mg/kg/week	3rd occurrence	0,1,2	4.5 mg/kg/week	-3
6 mg/kg/week	4th occurrence	any	Stop Treatment	-
4.5 mg/kg/week	4th occurrence	any	Stop Treatment	-

[a] Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks

Arm B (6 mg/kg/week)[b]				
Dose	**Occurrence**	**Recovery to grade**	**Dose Reduction to**	**Dose Level (DL)**
Delay treatment, re-assessment after 1-2 weeks[c]				
6 mg/kg/week	1st occurrence	0,1	No change	-
6 mg/kg/week	1st occurrence	2	4.5 mg/kg/week	-1
6 mg/kg/week	2nd occurrence	0,1,2	4.5 mg/kg/week	-1
4.5 mg/kg/week	2nd occurrence	0,1,2	3 mg/kg/week	-2
4.5 mg/kg/week	3rd occurrence	0,1,2	3 mg/kg/week	-2
3 mg/kg/week	3rd occurrence	0,1,2	1.5 mg/kg/week	-3
3 mg/kg/week	4th occurrence	any	Stop Treatment	-
1.5 mg/kg/week	4th occurrence	any	Stop Treatment	-

[b] Dose Reductions for 9 mg/kg loading not applicable

[c] Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks

6.2.4.3 Occurrence of Infusion-related Reactions

Premedication to avoid or minimize infusion-related reaction of Sym004 is mandated during the treatment period in this trial. The following premedication regimen is mandatory before the first 4 Sym004 infusions:

- Glucocorticoid equivalent to 80 to 100 mg methylprednisolone, IV one-half to 2 hours before Sym004 infusion
- Antihistamine (H1 antagonist), e.g., diphenhydramine 25 to 50 mg or similar, IV one-half to 2 hours before Sym004 infusion.

At subsequent infusions, premedication is at the investigator's discretion.

If infusion-related reaction occurs, it should be classified according to NCI-CTCAE (v4.03) and the guideline shown in Table 6-4 should be followed.

Table 6-4 Management of Infusion-related Reactions

Grade of Infusion-related Reaction[a]	Treatment of Infusion-related Reaction
1	• Continue infusion • Monitor closely
2	• Stop Sym004 infusion • Apply symptomatic treatment, e.g., antihistamines, NSAIDs • Use supportive treatment, e.g., bronchodilator, oxygen, etc., if necessary. • When symptoms have resolved and the subject is clinically stable, restart infusion at 15 mL/hour and monitor vital signs closely for at least 15 minutes • If vital signs remain stable, double the infusion rate every 15 minutes, e.g., 15 to 30 mL/hour, 30 to 60 mL/hour, and 60 to 90 mL/hour or 120 mL/hour • Monitor closely • If symptom reoccurs; stop the infusion, instigate remedial therapy, monitor closely, and evaluate whether the subject is eligible to continue the trial
3	• Stop Sym004 infusion • Apply both symptomatic and supportive treatment, e.g., bronchodilator, antihistamines, glucocorticoids, i.v. fluids, oxygen, etc., as needed • Withdraw the subject from treatment
4	• Stop Sym004 infusion immediately • Apply necessary life-support treatment as needed • Withdraw the subject from the treatment

CTCAE=Common Terminology Criteria for Adverse Events; i.v.=intravenous: NSAIDs= non-steroidal anti-inflammatory drugs.
a According to NCI-CTCAE (Version 4.03). See Section 12, Appendix B.

6.2.4.4 Hypomagnesaemia

Subjects receiving Sym004 will be monitored weekly for hypomagnesemia. Hypomagnesaemia should be treated according to the following criteria:

- Grade 1/2 – no replacement therapy required, weekly monitoring is required.
- Grades 3/4 – IV treatment with $MgSO_4$ 6 to 10 g minimum 2 times per week. Electrocardiogram (ECG) is required before Sym004 administration to monitor QT prolongation that may result in severe arrhythmias such as TdP. In case of TdP arrhythmias or other life-threatening cardiac arrhythmias, subjects must be discontinued from Sym004 treatment.

6.3 Assignment to Treatment Groups

Randomization by a central interactive web response system (IWRS) should be carried out within 2 weeks after the subject undergoes screening (+ 1 week in case of medical issues, + 2 weeks if biopsy obtained) and becomes eligible for the trial participation. Administration of Sym004 at the assigned dose level or of Investigator's choice treatment should occur on the same day of randomization or no later than 72 hours after randomization.

The first DMC meetings will take place after 6 and after 12 subjects in each experimental arm have completed at least one cycle of treatment (defined as 3 weeks). In case subjects were randomized and did not receive Sym004, additional patients will be allocated manually to the respective treatment group prior to these first two DMC meetings.

Further statistical considerations regarding randomization are discussed in Section 8.2.

6.4 Prophylactic and Reactive Treatment of Sym004-Induced Skin Toxicities

Subjects in the Sym004 arms are to receive mandatory prophylactic treatments for acneiform rash as described in Table 6-5.

Table 6-5 Mandatory Prophylaxis for Skin Toxicities

Treatment	Dose	Start	Stop	Alternatives
SYSTEMIC THERAPY[a]				
Minocycline OR Doxycycline	1 x 100 mg/day 2 x 100 mg/day	Day 1	Day 60[b]	In case of intolerance: • First generation cephalosporins • Amoxycillin • Erythromycin • Limecycline
TOPICAL THERAPY				
Low potency steroid creams such as (but not limited to): • Alclometasone 0.05% • Desonide 0.05% • Fluocinolone 0.01%	2 x daily on face and chest	Day 1	Day 60	
Moisturizer (creams or ointments)	3 x daily to the hands, and after hand washing[c] 2 x daily on the rest of the body	Day 1	Continue	

a If infection is suspected (yellow crusts, purulent discharge, painful skin / nares), obtain culture and change to oral antibiotic based on sensitivities.

b May be continued beyond Day 60 at the Investigator's discretion or in the event of CTCAE Grade 2 rash.

c Use fragrance-free soap.

NCI-CTCAE Grade 1 – 3 Sym004-induced skin toxicities (i.e., rash, xerosis, paronychia, pruritus, fissures, and photosensitivity) should be managed according to the rules summarized in Table 6-6 to Table 6-11.

Dose delays and reductions for CTCAE Grade 3 skin toxicity should be implemented according to the dose level and the instructions provided in Table 6-4 (Section 6.2.4.2). In each case, the next treatment should be delayed and the subject's condition should be re assessed after 1-2 weeks. Treatment should be delayed further in the event that the toxicity remains at Grade 3 after 2 weeks.

Subjects must be withdrawn from Sym004 treatment in case of Grade 4 skin toxicity.

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

Table 6-6 Treatment of Sym004-induced Rash

CTCAE Grade 1	Action with Sym004	Treatment
Papules and/or pustules covering **< 10% BSA**, which may or may not be associated with symptoms of pruritus or tenderness	Continue at same dose	**Topical:** • Steroid creams of low potency (alclometasone 0.05%, desonide 0.05% or fluocinolone 0.01%), 2 x daily, face + chest • Moisturizers, 2 x daily, rest of body **Systemic[a]:** • Minocycline 100 mg/day or doxycycline 200 mg/day at least 4 weeks
CTCAE Grade 2	**Action with Sym004**	**Treatment**
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; limiting instrumental ADL	Continue at same dose	**Topical:** See Grade 1 **Systemic[a]:** • 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
CTCAE Grade 3	**Action with Sym004**	**Treatment**
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	**Delay 1-2 weeks, continue skin treatment and re-assess[b]** Dose reduction acc. to instructions in table 6-3 in case of: • 1st occurrence if recovered only to Grade 2 • 2nd and 3rd occurrence Stop of treatment in case of 4th occurrence	**Topical:** See Grade 1 **Systemic[a]:** See Grade 2

ADL=activities of daily living; BSA=body surface area; DL=dose level.

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

b Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks.

Table 6-7 Treatment of Sym004-induced Xerosis

CTCAE Grade 1	Action with Sym004	Treatment
< 10% BSA and no associated erythema or pruritus	Continue at same dose	**Topical:** **Face:** Moisturizing cream or ointment[a] 2 x daily AND **Body:** Ammonium lactate 6-12% 2 x daily
CTCAE Grade 2	**Action with Sym004**	**Treatment**
10 to 30% BSA and associated with erythema or Pruritus limited instrumental ADL)	Continue at same dose	**Topical:** **Face:** Moisturizing cream or ointment[a] 2 x daily AND **Body:** Ammonium lactate 12% cream OR salicylic acid 3-6% cream OR urea cream 10-20% 2 x daily
CTCAE Grade 3	**Action with Sym004**	**Treatment**
> 30% BSA and associated with pruritus; limiting self care ADL	**Delay 1-2 weeks, continue skin treatment and re-assess[b]** Dose reduction acc. to instructions in table 6-3 in case of: • 1st occurrence if recovered only to Grade 2 • 2nd and 3rd occurrence Stop of treatment in case of 4th occurrence	**Topical:** **Face:** Moisturizing cream or ointment[a] 2 x daily AND **Body:** Ammonium lactate 12% cream OR salicylic acid 3-6% cream OR urea cream 10-20% 2 x daily AND Eczematous areas: topical steroid (e.g., triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05% cream, fluticasone propionate 0.05%) to 2 x daily

ADL=activities of daily living; BSA=body surface area; DL=dose level.

a If prescription not available, recommendation by pharmacist is acceptable.

b Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks.

Table 6-8 Treatment of Sym004-induced Paronychia

CTCAE Grade 1	Action with Sym004	Treatment
Nail fold edema or erythema; disruption of the cuticle	Continue at same dose	• Topical antibiotics (e.g., clindamycin 1%, erythromycin 1%) AND • Vinegar soaks (i.e., soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day) AND • Bacterial culture (oral antibiotic if infection confirmed)
CTCAE Grade 2	**Action with Sym004**	**Treatment**
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	Continue at same dose	Same as for Grade 1 AND • Silver nitrate application weekly (needs consultation with dermatologist or surgeon)
CTCAE Grade 3	**Action with Sym004**	**Treatment**
Surgical intervention or i.v. antibiotics indicated; limiting self care ADL	**Delay 1-2 weeks, continue skin treatment and re-assess[a]** Dose reduction acc. to instructions in table 6-3 in case of: • 1st occurrence if recovered only to Grade 2 • 2nd and 3rd occurrence Stop of treatment in case of 4th occurrence	Same as for Grade 1 AND • Silver nitrate application weekly (needs consultation with dermatologist or surgeon) AND • Consider nail avulsion (needs consultation with dermatologist or surgeon)

ADL=activities of daily living; DL=dose level; i.v.=intravenous.

a Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks.

Table 6-9 Treatment of Sym004-induced Pruritus

CTCAE Grade 1	Action with Sym004	Treatment
Mild or localized; topical intervention indicated	Continue at same dose	• Topical steroid (e.g., triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05% cream, Fluticasone propionate 0.05%), 2 x daily OR • Topical antipruritics (pramoxine 1%, doxepin 5% cream), 2 x daily
CTCAE Grade 2	**Action with Sym004**	**Treatment**
Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Continue at same dose	Same as for Grade 1 AND • Oral antihistamines (diphenhydramine 25-50 mg; hydroxyzine 25 mg; fexofenadine 60 mg 3 x daily)
CTCAE Grade 3	**Action with Sym004**	**Treatment**
Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	**Delay 1-2 weeks, continue skin treatment and re-assess**[a] Dose reduction acc. to instructions in table 6-3 in case of: • 1st occurrence if recovered only to Grade 2 • 2nd and 3rd occurrence Stop of treatment in case of 4th occurrence	Same as Grade 2

ADL=activities of daily living; DL=dose level.

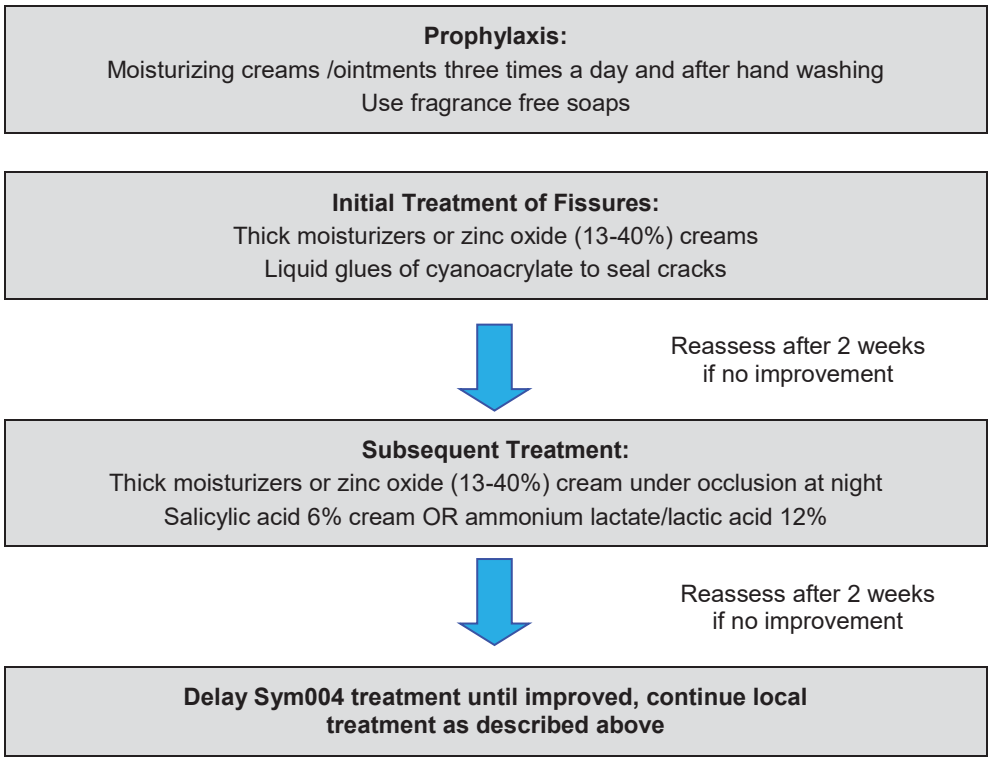
a Longer treatment delays allowed if no recovery to ≤ Grade 2 after 2 weeks.

Table 6-10 Treatment of Sym004-induced Photosensitivity

CTCAE Grade 1	Action with Sym004	Treatment
Painless erythema and erythema covering **< 10% BSA**	Continue at same dose	Broad spectrum sunscreen with an SPF of at least 15; need to be applied every 2 hours or more frequently if swimming or sweating
CTCAE Grade 2	**Action with Sym004**	**Treatment**
Tender erythema covering **10-30% BSA**	Continue at same dose	Broad spectrum sunscreen with a SPF sun protection factor ≥ 15 AND Topical corticosteroids (e.g., triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05% cream, fluticasone propionate 0.05%), 2 x daily
CTCAE Grade 3	**Action with Sym004**	**Treatment**
Erythema covering **> 30% BSA** and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	**Delay 1-2 weeks, continue skin treatment and re-assess**[a] Dose reduction acc. to instructions in table 6-3 in case of: • 1st occurrence if recovered only to Grade 2 • 2nd and 3rd occurrence Stop of treatment in case of 4th occurrence	Same as Grade 2

BSA=body surface area; DL=dose level; NSAIDs=nonsteroidal anti-inflammatory drugs; SPF=sun protection factor.

Table 6-11 Treatment of Sym004-induced Fissures



In addition, subjects experiencing Grade 3 or 4 hypomagnesemia are to receive IV $MgSO_4$ 6 to 10 g at least twice weekly until symptoms resolve (see Section 6.2.4.4).

These drugs can be sourced from the market and are thus not provided by the sponsor.

No other drugs are mandated by the protocol.

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines

Any medications (other than those excluded by the protocol [i.e., nonpermitted medicines as described in Section 6.5.2]) that are considered necessary for the subjects' welfare and will not interfere with the IMP may be given at the investigator's discretion. This includes analgesics, antiemetics, laxatives, medications for constipation, and bisphosphonates.

Furthermore, the following are allowed during the trial:

- Correction of electrolyte deficiency
- Radiotherapy for pain control against nontarget lesions as long as it does not influence bone marrow function
- Total tumor resection in responding subjects who have become candidates for curative resection
- Skin toxicity management according to the above recommendations, including topical steroid- and antibiotic-containing creams, oral steroids, and systemic antibiotics (see Section 6.5.3.2)

The investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF noting the generic name of the medication or brand name as well as the route of administration, duration, and indication.

Medications may be administered for the management of symptoms associated with the administration of Sym004 as required. These might include analgesics, anti-nausea medications, anti-histamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

6.5.2 Nonpermitted Medicines

Usage of the following medications and therapies are not allowed during the trial:

- Any anti-cancer treatment including cytotoxic or cytostatic agents, hormonal therapy (except as physiologic replacement), other anti-EGFR antibodies or anti-EGFR small molecule inhibitors
- Immunosuppressive drugs except

  - glucocorticosteroid treatment administered with a daily dose of ≤ 20 mg prednisolone or equivalent, and
  - for treatment of infusion-related events, for premedication, or for treatment of Sym004-induced skin toxicities
- Radiotherapy against the target lesion(s)
- Azithromycin and other drugs with the potential to cause QT prolongation
- Major surgery, which precludes the subject from complying with the requirements of the protocol

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, e.g., because of AEs or disease progression, the subject in question will be withdrawn from the trial, and the subject's data that will have been obtained before the withdrawal may be used for safety and efficacy evaluations.

6.5.3 Other Trial Considerations

6.5.3.1 Premedication for Infusion-related Reactions

Refer to Section 6.2.4.3.

6.5.3.2 Premedication for EGFR-associated Skin Toxicity

Prophylactic strategy to prevent and/or minimize the EGFR-related skin toxicity is applied in this clinical trial of Sym004. Refer to Table 6-5.

6.5.4 Special Precautions

Not applicable.

6.6 Packaging and Labeling

Sym004 is a 5.0 mg/mL solution for IV infusion packaged in glass vials (Type 1) with a fill volume of 30 mL.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines.

Sym004 will be packed in boxes containing a suitable number of vials. Labeling may include the following information: Investigational New Drug (IND) statement, trial number, product code, number of vials per box, route of administration, batch number, storage condition, vial number range and details of the Sponsor. Additional information or modifications may occur locally.

Sym004 will be shipped in a suitable transport cool container (2°C to 8°C) that is monitored with a temperature data-logger.

6.7 Preparation, Handling, and Storage

Sym004 is intended for single use and should be stored at 2°C to 8°C. The product must be protected from direct sunlight and must not be frozen. Since Sym004 does not contain preservatives, any unused portion remaining in the vial must be discarded.

Sym004 will be diluted in saline before administration (Sym004 is administered by IV infusion). The volume of saline depends on the dose level: 500 mL for dose levels of 6 mg/kg or lower, 1000 mL for dose levels of 9 to 18 mg/kg). All handling and preparation of IMP should take place at the pharmacy of each trial site.

The investigator is responsible for informing the pharmacy of the dose of Sym004 administered to the subject with the subject's body weight. Every dose must be prepared according to the recent body weight captured every 3 weeks.

Preparation of the infusion bag should be done immediately before the infusion start. The infusion must be completed within 8 hours after preparation.

If the administration of Sym004 cannot be completed within 8 hours after preparation, a new infusion bag must be used.

6.8 Investigational Medicinal Product Accountability

The investigator is responsible for ensuring accountability for the IMP, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of the IMP, the investigator (or designee) will check for accurate delivery and acknowledge receipt by registering the shipment as received in IWRS, signing (or initialing) and dating the documentation provided by the sponsor or designee and returning it to the sponsor or designee. A copy will be retained for the Investigator File.
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the sponsor and an accurate accounting will be available for verification by the sponsor's monitor at each monitoring visit.
- IMP accountability records will include:
    - Confirmation of the IMP delivery to the trial site
    - The inventory at the site of IMP provided by the sponsor and prepared at the site
    - The use of each dose by each subject
    - The return to the sponsor or alternative disposition of unused IMP
    - Dates, quantities, batch numbers, use by dates and (for IMP prepared at the site) formulation, as well as the subjects' trial numbers

- The Investigator should maintain records that adequately document
    - that the subjects were provided the doses specified by the clinical trial protocol/amendment(s), and
    - that all IMP provided by the sponsor was fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. The IMP that has been dispensed to a subject must not be redispensed to a different subject.

The sponsor's monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for the return to the sponsor or authorizing their destruction by the trial site.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the trial site at every visit when the IMP administration is planned (hereinafter called treatment visit). In order to allow the assessment of compliance with trial treatment, administration of the IMP should be recorded in the medical records and the corresponding section of the eCRF.

6.10 Method of Blinding

This phase II trial is not a blinded trial as the incidence of rash (approximately 95%) for Sym004 does not allow true blinding.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

There is no known antidote for Sym004. In the event of overdose of Sym004, subjects should receive appropriate supportive medical care at the investigator's discretion and be followed up carefully.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or nonserious) – must be reported to the sponsor's Global Drug Safety department or its designated representative in an expedited manner using the SAE Report Form (without indicating a serious criterion if not applicable) (see Section 7.4.1.4).

6.13 Medical Care of Subjects After End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments is provided in Section 12, Appendix D**.**

All efforts should be made to perform assessments as close as possible to the scheduled time points. Examinations performed before the signature of the ICF by the subject, which are part of the routine workup for subjects in the target population, can be accepted provided they are in the screening timeframe defined in the clinical trial protocol.

7.1.1 Screening Period

Prior to performing any trial assessments, the investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

On the basis of the findings obtained during the screening period, the investigator will decide whether the subject is eligible for the trial. Scheduled screening assessments in all subjects are as follows:

- Provision of written informed consent and review of inclusion and exclusion criteria
- Documentation of demographics, relevant medical history, concomitant medication
- Prior cancer treatment (surgery and/or radiotherapy for CRC; chemotherapy and biologic targeted therapy for CRC with start and stop dates, and reason for stopping; previous anti-EGFR mAb treatment, start date, stop date, best response, reason for stopping, most recent date of progression on anti-EGFR mAb; other investigational procedures if any)
- Tumor histology, mutation status, location, and extent of disease (primary tumor location, KRAS and BRAF status at initial diagnosis (if available), tumor histology
- Safety laboratory (hematology: red blood cells, white blood cells, neutrophils, platelets, hematocrit, and haemoglobin; biochemistry: creatinine, creatinine clearance calculated according to Cockcroft-Gault, sodium, potassium, calcium, magnesium, glucose, albumin, ALAT, ASAT, alkaline phosphatase, total bilirubin, CRP, blood urea, INR, activated partial thromboplastin time (aPTT), pregnancy test [if applicable])
- PK blood sampling
- ADA blood sampling
- Baseline Safety (symptoms and persisting toxicities from prior therapy to check compliance with inclusion criteria)

- Serology testing for hepatitis B, hepatitis C, and human immunodeficiency virus
- Tumor assessment (computed tomography [CT] scan or magnetic resonance imaging [MRI] of the thorax, pelvic region, and abdomen; tumor burden evaluation per RECIST v1.1)
- Physical examination including assessment of vital signs (blood pressure, heart rate, body temperature), body weight, height, ethnicity, dermatological examination (CTCAE v4.03 scaling)
- ECOG performance status
- 12-lead ECG

If all eligibility criteria are met and screening procedures are completed:

- Tumor biopsy (voluntary or mandatory [dedicated centers only] tumor biopsy) including but not limited to RAS and RAF pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels;
- Exploratory biomarker evaluation will include but not be limited to the following: RAS pathway mutations, HER2 and MET amplification in circulating DNA (if technically feasible), EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels.

7.1.2 Randomization

Randomization by IWRS should be carried out within 2 weeks after the subject undergoes screening (+ 1 week in case of medical issues, + 2 weeks if biopsy was obtained) and becomes eligible for the trial participation.

Randomization into the trial will be suspended and no more patients dosed after the first 6 patients in each experimental arm will be recruited into the trial. Randomization will be resumed only once the DMC will issue a recommendation to resume randomization. The same process will be followed once the first 12 patients will have been recruited in each experimental arm into the trial.

7.1.3 Treatment Phase

Upon entering the Treatment Phase, randomized subjects will receive IV administration of Sym004 at the assigned dose level (Arm A: 12 mg/kg/week, or Arm B: 9 mg/kg loading, 6 mg/kg/week thereafter), or the investigator's choice treatment (Arm C: BSC, 5-FU, or capecitabine). This should occur on the same day of randomization, but no later than 72 hours after randomization. Treatment will continue until significant clinical progression, occurrence of unacceptable toxicity, or withdrawal of consent.

The following assessments are to be performed according to the following schedule during the Treatment Phase in all subjects:

- Physical examination (normal/abnormal, weight) – q3w

- Vital signs (body temperature, heart rate, and blood pressure [systolic and diastolic] after 5 minutes supine) – q1w (Arms A and B), q3w (Arm C)
- Dermatological examination (complete skin examination [NCI-CTCAE v4.03 scaling]), report on compliance to prophylactic and reactive measures – q1w (Arms A and B only), q3w (Arm C)
- 12 lead ECG – q3w and in case of hypomagnesemia Grade ≥ 3 toxicity
- ECOG performance status – q3w
- Laboratory tests local (hematology, coagulation, and serum chemistry) – q3w; laboratory tests, (magnesium) – q1w (Arm A+B only), q3w (Arm C)
- Pharmacokinetics (PK sampling point: preparation of 2 serum aliquots)
    - PK blood sampling:
        - Week1 Day 1: Within 30 minutes before infusion, at end of the initial 1-hour infusion, and at 0.5, 1, 2, 4 hours after infusion.
        - Days 8, 15, 29, 43: Within 30 minutes before infusion (trough value) and immediately after infusion (peak value)
- ADA (ADA sampling point: preparation of 2 serum aliquots)
    - ADA blood sampling :
        - Days 15, 29, and 43, every 2 weeks (q2w); days 78, 120, and 162 every 6 weeks (q6w) : Within 30 minutes before infusion
- Tumor assessment (imaging of chest, abdomen and pelvis) – q6w
- Pregnancy Test (Urine) – q3w (if applicable)
- AEs (signs and symptoms) – q1w (telephone for Arm C)
- Concomitant medications (all concomitant medications including prophylactic use of antibiotics) – every 3 weeks (q3w)
- Quality of life (EORTC QLQ-C30 (v3) + EORTC QLQ-CR29 (q6w)); FACT-EGFR 18 Questionnaire) – q3w

7.1.4 End of Treatment Visit

The end of treatment visit will be performed within 5 days after discontinuation of trial treatment (e.g., within 5 days after the decision to discontinue trial treatment has been taken). Subjects who discontinue the treatment due to any reasons other than PD, should continue to attend the tumor assessment visits until PD has been observed.

This visit includes:

- Physical examination, weight, vital signs
- ECOG PS

- ECG
- Blood sampling for safety laboratory (hematology, biochemistry, coagulation)
- PK/ADA
- Tumor assessment
- AEs
- Concomitant medications/procedures
- Pregnancy test (urine) – q3w (if applicable)

7.1.5 End of Trial Intervention Visit

The end of trial intervention visit should be scheduled after assessment of PD, but no earlier than 28 days after stop of treatment. This is also to be performed for subjects stopping trial intervention for reasons other than PD. Subjects with an ongoing treatment-related SAE or an ongoing Grade 3/4 hypomagnesemia or any significant ongoing treatment related AE must be followed up until the SAE/AE has resolved, is considered stable, or is not considered to be clinically relevant by the Investigator. After this visit no further trial-related assessments occur and survival and disease follow-up starts.

This visit includes physical examination, vital signs, documentation of AEs, and concomitant medication.

7.1.6 End of Trial Visit

Follow-up for progressive disease, survival, and further antitumor treatments will be performed as described below until the end of trial visit.

Progressive Disease Follow-up

For subjects who discontinue the trial due to any reasons other than PD, information on the time point of subsequent disease progression (clinical or radiological) must be provided.

Survival Follow-up

Subjects discontinuing treatment due to PD or for any other reason will be followed up for survival (e.g., by phone or clinic visits) and information on further antitumor treatments every 6 weeks (± 1 week) until the end of trial.

7.1.7 Examinations and Assessments

Examinations and assessments will be conducted in each of the visits as planned in Sections 7.1.1 to 7.1.6 (for details, see Section 12 Appendix D).

Prior to performing any trial assessments not part of the subject's routine medical care, the investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

The anticipated total volume of blood to be drawn for the laboratory tests, immunogenicity analysis, and PK analysis is provided as an example in Table 7-2.

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening Period.

7.2.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier
- Date of birth
- Sex
- Race

7.2.2 Diagnosis of Tumor

The tumor disease information that will be documented and verified at the screening visit for each subject includes the following:

- Primary tumor location
- RAS and BRAF status at initial diagnosis (if available)
- Tumor histology

Prior cancer treatment information that will be documented and verified at the screening visit for each subject includes the following:

- Surgery and/or radiotherapy for CRC
- Chemotherapy and biologic targeted therapy for CRC with dates of start and stop, and reason for stopping
- Previous anti-EGFR mAb treatment, start date, stop date, best response, reason for stopping, most recent date of progression on anti-EGFR mAb
- Other investigational procedures if any.

7.2.3 Medical History

To determine the subject's eligibility for the trial, a relevant medical history of each subject will be collected and documented during screening, which will include, but may not be limited to, the following:

- Past and concomitant nonmalignant diseases and treatments
- All medications taken and procedures carried out within 30 days prior to screening

For trial entry, all the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.4 Vital Signs and Physical Examination

Vital signs including body temperature, heart rate (after 5-minute rest), and blood pressure (after 5-minute rest) will be recorded at trial entry.

A complete physical examination will be performed.

The ECOG performance status will be documented during the Screening Period.

Body weight and height will be recorded.

7.2.5 CT or MRI Scans for Tumor Assessment at Baseline

Computed tomography with or without MR imaging of the chest, abdomen, and pelvis must be performed within 28 days prior to first treatment. Imaging must be performed with contrast and baseline status of the tumor disease using RECIST v1.1. Additional imaging (such as bone scan) must be performed when other areas of disease are suspected. None of these investigations need to be repeated if they were done within 4 weeks prior to enrollment.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at screening after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR and QT intervals, and possible arrhythmias.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the trial, but also as verification that each enrolled subject fulfills all the trial entry criteria and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3.2. A detailed description of laboratory assessments is provided in Section 7.4.3. Blood samples for serology and tumor tissue will be collected for biomarker analysis.

7.3 Assessment of Efficacy

The efficacy (antitumor activity) of Sym004 will be assessed by the investigator according to the RECIST v1.1 (see Section 12 Appendix A).

The following parameters are used for assessment of efficacy:

- Overall survival
- Progression-free survival time
- Best overall response per RECIST v1.1 (confirmed CR or PR)
- Time to treatment failure

7.4 Assessment of Safety

The safety profile of Sym004 will be assessed through the recording, reporting, and analyzing of baseline medical conditions; AEs, physical examination findings including vital signs; and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the investigator or reported by the subject (see Section 7.4.1.2).

The reporting period for AEs is described in Section 7.4.1.3.

In addition, an independent Data Monitoring Committee (DMC) will meet after 6 and after 12 subjects in each experimental arm (Arm A Sym004 at 12 mg/kg/week, Arm B Sym004 at 9 mg/kg loading followed by 6 mg/kg/week maintenance) have completed at least one cycle of treatment (defined as 3 weeks). During the data review, the enrollment of further subjects will be suspended. The DMC will review all emergent safety data and will evaluate whether there is any evidence for excess of toxicity compared to data derived from previous trials Sym004-01 and Sym004-02. The DMC will provide a recommendation on whether to continue the trial unchanged, continue with changes (which might include extension of the monitoring period, further DMC meetings, discontinuation of one dose, exploration of a lower dose) or discontinue. No further patients will receive the investigational product until the recommendation of the DMC will be issued and processed.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, 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 a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

The investigator is required to grade the severity/intensity of each AE.

Investigators will reference the NCI-CTCAE v4.03 (publication date: 14 June 2010) for grading the severity of AEs.

A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event Grades are also provided.

If a particular AE's severity/intensity is not specifically Graded by the guidance document, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

- **Grade 1:** Mild
- **Grade 2:** Moderate
- **Grade 3:** Severe
- **Grade 4:** Life-threatening or disabling
- **Grade 5:** Death related to AE*

According to the sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the investigator must also report the event as an SAE (see definition below) as per Section 7.4.1.4. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

*Note: Death (Grade 5 as defined by NCI-CTCAE v4.03) is mainly regarded as an outcome, to be documented as described below.

In the case of death, the primary cause of death (the event leading to death) should be recorded and reported as a SAE; "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMPs (Sym004 and comparator) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMPs include, but may not be limited to, temporal relationship between

the AE and the trial treatments, known side effects of the IMPs, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not suspected to be reasonably related to the IMP. The AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to the IMP. The AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose

- Results in death,
- Is life-threatening.

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a SAE and all such cases should be reported in an expedited manner as described in Section 7.4.1.4.

Events that do not Meet the Definition of a SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events not to be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

Progression of underlying disease is not an AE and therefore not a SAE per se.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs and reported as SAEs if any seriousness criteria are met.

Predefined AEs of Special Interest for Safety Monitoring

No predefined AEs of special interest for safety monitoring exist in this trial.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. Subjects of Arm C will be queried additionally via phone mirroring the weekly visit schedule. During the reporting period of the trial, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs must be additionally documented and reported using an Serious Adverse Event (SAE) Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMPs), and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through end of trial intervention visit. The subject should be withdrawn from this study prior to be enrolled in another study or treated with non-permitted anticancer treatment (see Section 5.5.1).

7.4.1.4 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the person(s) identified in the SAE Report Form (Clinical Trials) or the clinical trial protocol by fax or by e-mail.

When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines are the same for any new follow-up information on a previously reported SAE.

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the SAE Report Form (Clinical Trials).

All written reports should be transmitted with the SAE Report Form (Clinical Trials), which must be completed by the investigator following specific completion instructions.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided, if available, e.g., laboratory results, hospital discharge summary, autopsy. In all cases, the information provided on the SAE Report must be consistent with the data on the event that are recorded in the corresponding sections of the eCRF.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, other records where needed) or to any question the sponsor/designee may have on the AE within the same timelines as described for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor and (as applicable) to allow the sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible monitor, although in exceptional circumstances, the CRO's Global Drug Safety department may contact the investigator directly to obtain clarification or to discuss a particularly critical event.

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

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC or IRB that approved the trial.

In accordance with ICH GCP guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the sponsor will provide appropriate safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any safety reports provided by the sponsor and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that directive and with the related detailed guidances.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the study (see Section 7.4.1.3) and are assessed for final outcome at the end of trial intervention visit. Any effort should be made to obtain the outcome of an event. All SAEs ongoing at the end of trial intervention visit must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and in female partners of male subjects. The investigator must notify the sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The investigator must notify the sponsor of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the SAE Report Form (Clinical Trials) when the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form when the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from IMP immediately. The sponsor must be notified without delay and the subject must be followed up as mentioned above.

7.4.3 Laboratory Assessments

It is essential that the sponsor or designee will be provided with a list of normal laboratory ranges prior to shipment of the IMP. Any change in normal laboratory ranges during the trial will additionally be forwarded to the sponsor or designee.

All routine laboratory analyses will be done at a laboratory facility local to the trial site, and relevant results should be available before dosing with IMP. The report of the results must be retained as a part of the subject's medical record or source documents.

Blood samples for the tests listed in Table 7-1 will be taken from nonfasted subjects during the Screening Period (Days -14 to -1); the Treatment Phase, end of treatment, and at the end of trial visit at the time points specified in Section 12 Appendix D.

Table 7-1 Required Laboratory Safety Tests

Serum Chemistry	Hematology
Albumin	
Alkaline phosphatase	Absolute neutrophil count
Alanine aminotransferase (ALT)	Hematocrit
Aspartate aminotransferase (AST)	Hemoglobin
Urea	Platelet count
Calcium	Red blood cells
Creatinine	White blood cells and differential count
Creatinine clearance (calculated)	
C-reactive protein (CRP)	
Glucose	
Magnesium	
Potassium	
Sodium	
Total bilirubin	
INR, Activated partial thromboplastin time (aPTT)	
β-hCG in female subjects (screening only)	Women of childbearing potential: Urine β-hCG in female subjects test (at screening, this test is replaced by serum β-hCG)

For women of childbearing potential (WOCBP), pregnancy testing (serum β-hCG) will be performed during the Screening Period. Subjects after menopause (age-related amenorrhea ≥ 12 consecutive months) or subjects who had undergone hysterectomy, are sexually inactive, or underwent bilateral oophorectomy are exempt from pregnancy testing.

Details on the blood volume to be drawn from each subject during screening, the Treatment Phase, and at end of treatment, and end of trial visit are presented in Table 7-2.

Table 7-2 Total Per Subject Blood Sampling Volume

Assessment	mL/ Time	Screening Period (at Screening Assessment)		Treatment Period[a]		Follow-up Period (at End of Trial Assessment)		Total	
		Times	mL	Times	mL	Times	mL	Times	mL
Hematology	2[b]	1	2	5	10	1	2	7	14
Clinical chemistry	5[b]	1	5	5	25	1	5	7	35
Serology	4[b]	1	4					1	4
Magnesium[c]	2[b]			9	18			9	18
Biomarker evaluation	30[b]	1	30					1	30
Pharmacokinetics[c]	5[b]	1	5	14	70	1	5	16	80
Blood samples for ADA[c]	5[b]	1	5	4	20	1	5	6	35
Total			**51**		**143**		**17**		**216**

a The Treatment Period cannot be fixed in advance; therefore, the times and volumes of blood collection are estimated until Week 13 (corresponding to median PFS time) and then the end of treatment assessment.
b Planned blood volume to be taken per test, per subject.
c For Arms A and B only.
Note: The anticipated blood volume for a subject on control arm, estimated until Week 13 and at end-of-treatment, is 113 mL.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Body temperature, blood pressure (BP), and heart rate will be measured. At treatment visits, they should be measured before each Sym004 administration.

The BP and heart rate measurements must be obtained after at least 5 minutes rest in supine position with the subject's arm unconstrained by clothing or other material.

7.4.4.2 Physical Examinations

Full physical examinations will be conducted every 3 weeks, before each Sym004 administration. The examination will include general appearance and the following body systems: lymph nodes, mouth and throat, lungs, cardiovascular system, abdomen, extremities, musculoskeletal system, neurological system and skin.

7.4.4.3 Body Measurement

Height will be measured at the screening assessment. Body weight will be measured at the screening assessment and q3w thereafter. The body weight measured at the three weekly visits will be used for dosing at the particular visit. If the subject's BMI exceeds 30, the investigator should use the adjusted body weight instead of the actual body weight for calculation of the Sym004 dose (see Section 6.2.4.1).

7.4.4.4 Concomitant Medication

The following information on any medications and treatments other than the IMP and premedication are recorded (includes prophylactic use of drugs for skin toxicity):

- Route of administration
- Start date
- Stop date of administration or ongoing at trial termination
- Daily dose
- Indication and reason for use

7.4.4.5 Heart Function Test

A standard 12-lead ECG will be conducted at the screening assessment and q3w before the IMP administration. An overall interpretation of the ECG will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable.

7.4.4.6 General Status

General status of the subjects should be assessed with ECOG performance status.

7.4.4.7 Imaging Test

The CT scan or MRI of the chest, upper abdomen including thorax, pelvic region, and abdomen will be conducted at the screening assessment. The second CT scan or MRI will be conducted at Week 7, and thereafter every 6 weeks until disease progression, or consent withdrawal occurs, or until the subject meets any of the criteria for trial discontinuation.

The use of IV contrast is at the discretion of the investigator; however, a consistent method must be used on subsequent examinations for any given subject.

Disease progression at baseline before Sym004 treatment initiation must be documented by CT scan or MRI. If such scans or images have been obtained within 28 days prior to treatment at Week 1, they can be used as baseline; otherwise, new baseline images must be obtained.

In case a subject shows intolerance to treatment with Sym004, disease progression, or a subject decides to withdraw from the trial for any reason or meets any of the criteria for treatment or trial

discontinuation, a CT scan or MRI should be conducted for the subject as soon as possible (preferably within 4 weeks). If the CT scan or MRI was done in association with withdrawal and administration of the last dose of Sym004, the CT scan or MRI should not be repeated at the first follow-up visit at 4 weeks after the last Sym004 administration.

7.4.4.8 Anti-EGFR-associated Skin Toxicity

The skin examination must be performed by the Investigator. Subjects in both Sym004 arms will undergo weekly skin examinations. All subjects will have skin examinations before starting the IMP administration at every q3w treatment visit.

If Grade 3 EGFR-associated skin toxicity according to NCI-CTCAE v4.03 is observed, dose modification of Sym004 will be applied (see Section 6.2.4.2).

7.5 Pharmacokinetics

7.5.1 Body Fluid(s)

Blood samples will be collected at the time points noted in Table 7-3. Blood should be drawn from a different IV line than the one used for the IMP administration. The total volume of blood to be drawn for the PK assessment is provided in Table 7-2.

Table 7-3 Time Points of Blood Sampling for Pharmacokinetics Analysis and ADA Blood Sampling

Trial Periods and Assessments	**Screening Within 14 days prior to Day 1**	**Treatment (Weekly Administration of Sym004) until Progressive Disease[a]**									**End of Treatment**
Week	**- 2 and -1 IWRS Randomize**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week Day		**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Visit Window (Days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	
30 minutes before infusion	X,Y	X	X	X,Y		X,Y		X,Y[a]			X,Y Time Equivalent to "before infusion"
End of infusion		X	X	X		X		X			
+0.5 hour		X									
+1 hour		X									
+2 hour		X									
+4 hour		X									

X = PK blood sampling; Y = ADA blood sampling
a ADA blood sampling after Week 7: q6w (Week 12, Week 18, Week 24, drug discontinuation [EOTV]).

7.5.2 Pharmacokinetic Calculations

Concentrations of Sym004 in blood will be determined by a validated bioanalytical method. Based on the concentrations determined, the following PK parameters for Sym004 will be calculated for each subject in the first and fourth administration of Sym004, respectively.

- Area under concentration-time curve (AUC) from start of first infusion to 168 hours ($AUC_{0\text{-}168h}$)
- Half-life ($t_{1/2}$)
- Clearance (CL)
- Volume of distribution (VD)

The following parameters will be calculated with all data:

- Maximum concentration (C_{max})
- Trough concentration (C_{trough})
- Time to reach C_{max} (t_{max})

The C_{max}, C_{trough}, and t_{max} will be estimated from raw data while $AUC_{0\text{-}168h}$, $AUC_{0\text{-}inf}$, CL, and $t_{1/2}$ will be estimated using noncompartmental modeling. Further parameters based on modeling technique may be derived.

7.6 Biomarkers/Pharmacogenetics

Exploratory biomarker evaluation will include but not be limited to the following: RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels.

7.7 Other Assessments

7.7.1 Quality of Life

Quality of life will be assessed using the FACT-EGFRI 18 Questionnaire (q3w) and the EORTC QLQ-C30 (v3) and EORTC QLQ-CR29 instruments (q6w).

The FACT-EGFR 18 Questionnaire is an 18-question form intended for subjects treated with EGFR inhibitors. This questionnaire will be administered every 3 weeks during the Treatment Period.

The EORTC QLQ-C30 and EORTC QLQ-CR29 instruments assess the quality of life of cancer subjects. These questionnaires will be administered every 6 weeks during the Treatment Period.

8 Statistics

8.1 Sample Size

This is an open label, randomized, 3-arm trial, where the subjects will be randomized in the ratio of 1:1:1 to 2 Sym004 doses (Arms A and B) and a control group (Arm C). Median overall survival time is expected to be 6 months in the control arm and 9.2 months in each of the Sym004 arms, i.e., a HR of 0.65. A total number of 181 events (67 in the control arm and 57 in each Sym004 arm) will give 80% power for each Sym004 arm to detect the assumed difference to the control arm in overall survival time with a 20% two-sided overall significance level, using a multiple comparison procedure developed by Dunnett. Using Schoenfeld's formula, the per-comparison significance level of 0.121 would correspond to a critical value of an observed HR of 0.756. A total number of 240 subjects (assuming a drop-out rate of 5%), recruited in 22 months, is expected to yield 181 events after a follow-up time of 9 months.

With a total of 181 events, the probabilities of observing specific hazard ratios are presented below. The table below shows the probability of observing a HR of less than 0.75 under different assumptions about the true HR.

	Probability to observe a HR < 0.75 (1 Sym004 arm against control)	Probability to observe a HR < 0.75 (at least 1 Sym004 arm against control)
Under H_0 (HR = 1)	0.055	0.10
Under H_1 (HR = 0.65)	0.79	0.90
HR = 0.9	0.16	0.25

8.2 Randomization

Subjects will be randomized in the ratio of 1:1:1 to 2 Sym004 doses (Arms A and B) and a control group (Arm C).

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint is OS time, which is defined as the time from randomization to the date of death. If a subject has not died, his survival time will be censored at the last date he was known to be alive.

The primary OS analysis will include all events (deaths) included in the database at the time of database lock, therefore including any events captured after the agreed cut-off date as described in Section 5.7.

8.3.2 Secondary Endpoints

- Best overall response according to RECIST v1.1,
- PFS time (PFS time is defined as the duration from randomization until first event, where an event can be a progression [radiological confirmed or clinical progression] or death due to any cause, where death will only be considered as an event if it occurs within 12 weeks after last tumor response assessment without progression)
- Time to treatment failure
- Relative dose intensity (the relative dose intensity of Sym004 is defined as the actual dose intensity divided by the planned dose intensity, in which the actual dose intensity is calculated by the accumulated dose of Sym004 divided by the treatment duration of Sym004)
- Pharmacokinetic profile
- Host immune response: ADA
- Biomarkers including but not limited to RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels
- Quality of life.

8.3.3 Safety Endpoint(s)

The safety endpoints for this study are:

- Occurrence and nature of AEs
- Discontinuation due to AEs
- Laboratory results
- Vital Signs
- ECOG
- ECG

8.4 Analysis Sets

Intention-to-Treat (Full Analysis Set)

The intent-to-treat (ITT) population will include all subjects who were randomized to the IMP. Analyses performed on the ITT set will take into account subjects' allocation to treatment groups as randomized and not as treated.

Per protocol

The per protocol population will include all randomized subjects (ITT set), excluding those who had at least one significant protocol deviation expected by the sponsor to have a potential impact on the efficacy outcomes of the study (e.g., incorrectly diagnosed, not receiving sufficient dose of study medication, actual control treatment different from intended control treatment).

Safety

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

8.5 Description of Statistical Analyses

8.5.1 General Considerations

The following descriptive statistics will be used to summarize the trial data per dose group on the basis of their nature unless otherwise specified:

- Continuous variables: number of nonmissing observations, mean, standard deviation, 25th and 75th percentile, median, minimum, and maximum
- Categorical variables: frequencies and percentages based on the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

Unless otherwise indicated, all analyses will be presented separately for each treatment group.

Data will be pooled across centers in order to provide overall estimates of treatment effects.

Further description of the statistical methods and analyses will be provided in the SAP.

8.5.2 Analysis of Primary Endpoint(s)

Primary analysis: To test the equality of OS time between treatment groups (Group A versus Group C and Group B versus Group C), applying the two-sided log-rank test based on the ITT set. Null-hypotheses to be tested are

- H_0: $\lambda_A(t) = \lambda_C(t)$ versus H_1: $\lambda_A(t)=\theta\lambda_C(t)$, $\theta \neq 1$, and
- H_0: $\lambda_B(t) = \lambda_C(t)$ versus H_1: $\lambda_B(t)=\theta\lambda_C(t)$, $\theta \neq 1$,

where $\lambda(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in treatment Groups A and B and control Group C.

Multiple comparison procedure developed by Dunnett will be used to adjust the significance level for multiple testing. Each of the 2 tests for comparison of Sym004 and control will be tested at a significance level of 0.121 to get an overall significance level of 0.2.

Assumption behind the statistical model used for testing the null hypotheses is that censoring is independent from event and/or baseline factors (uninformative censoring). Informative censoring is not expected and no imputation for missing data will be done.

Kaplan-Meier estimates and median survival times will also be calculated. The 95% CIs for survival rates will be based on standard errors using Greenwood's formula and the CIs for the median calculated according to Brookmeyer and Crowley (10), (8).

Subgroup analyses will be performed for subjects with left- and right-sided colorectal cancer, respectively. Left-sided tumors are assumed to have a higher EGFR dependence and overall survival is expected to be longer for subjects when receiving Sym004. Furthermore, subgroup analyses will be performed on the basis of subjects' biomarker data, and may include analyses of subjects with RAS mutations and RAS wild-type, high and low protein expression of HER family ligands, HER2 expression and/or amplification positive and negative, MET expression and/or amplification positive and negative, and other potential biomarkers.

8.5.3 Analysis of Secondary Endpoint(s)

Best overall response by RECIST v1.1 will be summarized for each treatment group by means of counts and percentages for the categories CR, PR, SD, and PD. In addition a dichotomization will be done, where subjects with CR or PR will be considered as responders. Proportions of responders will be presented for each arm including corresponding 95% exact confidence intervals using the F-distribution method given by Collett (11), Clopper-Pearson (12).

Other endpoints (Relative Dose Intensity until PD, Pharmacokinetic Profile, Host immune response: ADA, Biomarkers (including but not limited to MET and HER2 amplification, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α and heregulin) protein expression in blood, RAS pathway mutations), quality of life) will primarily be summarized by use of descriptive statistics,

i.e., number of subjects (N), mean, median, standard deviation, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum for continuous variables and counts and percentages for categorical variables.

8.5.4 Safety Analyses

Safety data will be descriptively analyzed using the safety population. The AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. Then, the incidence and type of the following AEs will be summarized by dose cohort according to MedDRA system organ classes and preferred terms:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events
- TEAEs related to the IMP
- TEAEs of Grade ≥ 3 according to NCI-CTCAE (v4.03)
- TEAEs of Grade ≥ 3 according to NCI-CTCAE (v4.03), which are related to the IMP administration
- TEAEs leading to death, dose modification, interruption of the trial medication, or discontinuation of the IMP administration

An AE will be considered as treatment-emergent if it occurred during or after the first IMP administration until 28 days after the last IMP administration. An AE that occurred before the first IMP administration and worsened thereafter will also be considered an AE. Worsening is to be reported as a new AE.

Incidence of TEAEs will be summarized by treatment arms according to the MedDRA system organ classes and preferred terms with numbers and percentages of subjects experiencing these events. In addition, all TEAEs will be tabulated by intensity and relationship to the IMP.

Vital signs and laboratory test results will be listed by dose cohort, subject, and visit (if applicable), and any values outside the normal ranges will be flagged. They will also be classified by grade according to NCI-CTCAE (v4.03). The worst on-trial Grade after the first dose of the IMP will be summarized.

Subjects who terminated treatment will be displayed in a by-subject listing and summarized by primary withdrawal reason and dose cohort.

All deaths and deaths within 30 days of the last dose of the IMP as well as reasons for death will be tabulated by dose cohort.

Drug exposures will be summarized by dose cohort.

Details will be provided in the Statistical Analysis Plan.

8.5.5 Analysis of Further Endpoints

Not applicable.

8.6 Interim Analysis

A data monitoring committee will be established to review all relevant safety and toxicity data of available subjects and issue recommendation for further conduct of the trial after the first 6 patients will be recruited in each experimental arm, after the first 12 patients will be recruited in each experimental arm and then on a regular basis.

8.7 Data Collection and Analysis Beyond Primary Analysis

After reaching the primary analysis milestone for the trial as defined in section 5.7, the sponsor may reduce study 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.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the investigator must ensure that only subjects who have given their informed consent are included into the trial.

In 1998, the US Food and Drug Administration (FDA) introduced a regulation (21 Code of Federal Regulations [CFR], Part 54) entitled “Financial Disclosure by Clinical Investigators.” For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP (named “covered trials” by the FDA), the investigator and all sub-investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the sponsor or the sponsor’s product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject’s participation in the trial is his/her written informed consent. The subject’s written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted

by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) will be provided by the sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the investigator, the ICF must be signed and personally dated by the subject and the investigator.

The signed and dated declaration of informed consent will remain at the investigator's site, and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

In this trial two different informed consents are in place: one for the sites in which voluntary tumor biopsies will be performed, and one for those selected sites which are committed to mandatory tumor biopsies.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The investigator will explain the changes to the previous version.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

For the storage of biological samples, e.g. of tumor tissue samples in a bio bank, specific means will be taken to ensure the subject's right to privacy and the pertinent guidance documents and regulations will be considered.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the sponsor or CRO. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial investigator caring for the affected subject. The investigator agrees to provide his or her emergency contact information on the card for this purpose. If the investigator is available when an event occurs, s/he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the investigators.

This trial provides for a Quintiles Medical Advisor to be available 24/7 for urgent contact. The Quintiles Medical Advisor will be available to discuss any issues related to this trial, from 'First Subject In' to 'Last Subject Out'. If the Quintiles Medical Advisor is not able to provide 24/7 services for a period longer than 2 hours (e.g., due to business travel) or during vacations, an adequate back-up will ensure 24/7 medical service continuity.

The 24 hour urgent medical contact telephone is **+1 973 659 6677**.

Alternatively, call **+1 570 819 8565.**

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating in the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (e.g., Subject Information and ICF) to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File with the sponsor.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version, and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

The investigator or designee will be responsible for entering trial data in the eCRF provided by the sponsor or CRO. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The sponsor or designee will be responsible for data processing, in accordance with the applicable data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. The PDF files of the eCRFs will be provided to the investigators at the completion of the trial.

10.2 Source Data and Subject Files

The investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Sex
- Height
- Weight

- Medical history and concomitant diseases
- Tumor histology, mutation status, location, and extent of disease
- Prior anti-cancer treatment
- Prior and concomitant therapies (including changes during the trial)
- Trial identification
- Date of subject's inclusion into the trial (i.e., date of giving informed consent)
- Subject number in the trial
- Subject number
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, and laboratory value listings. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the investigator.

10.3 Investigator Site File and Archiving

The investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the monitor, and must be ready for sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the investigator must notify the sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH

GCP guidelines, whichever is longer. In any case, the investigator should ensure that no destruction of medical records is performed without the written approval of the sponsor.

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The site monitor will perform visits to the trial site at regular intervals.

Representatives of the sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the eCRFs, the IMP(s), and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the sponsor or designee in consultation with the coordinating investigator.

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites.

The investigator will inform the sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require presubmission review by the sponsor.

The sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

11 References

(1) WHO, International Agency for Research on Cancer. Globocan 2008.

(2) Engstrom PF, Arnoletti JP, Benson AB 3rd, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw 2009;7:778-831.

(3) 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 Jan 15; 70(2):588-597.

(4) Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer. N Engl J Med 2008;359:1757-1765.

(5) Rajput A, Koterba AP, Kreisberg JI, Foster JM, et al. A novel mechanism of resistance to epidermal growth factor receptor antagonism in vivo. Cancer Res 2007;67(2): 665–673.

(6) Dienstmann R, Tabernero J, Van Cutsem E, et al. Proof-of-concept study of Sym004, an anti-EGFR monoclonal antibody (mAb) mixture, in subjects (pts) with anti-EGFR mab-refractory KRAS wild-type (wt) metastatic colorectal cancer (mCRC). J Clin Oncol 2013; (suppl; abstr 3551).

(7) Lacouture M, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a Phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. Journal of Clinical Oncology, Vol 28, No 8 (March 10), 2010: pp. 1351-1357.

(8) Bendell JC, Ervin TJ, Senzer NN, et al. Results of the X-PECT study: A phase III randomized double-blind, placebo-controlled study of perifosine plus capecitabine (P-CAP) versus placebo plus capecitabine (CAP) in patients (pts) with refractory metastatic colorectal cancer (mCRC). ASCO 2012.

(9) Collett D. (1994), Modeling Survival Data in Medical Research, London: Chapman & Hall.

(10) Brookmeyer R and Crowley J. (1982), A Confidence Interval for the Median Survival Time, Biometrics, 38, 29–41.

(11) Collett D. (1991), Modelling Binary Data, London: Chapman & Hall.

(12) Clopper CJ and Pearson ES (1934),“The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial”, Biometrika 26, 404–413.

12 Appendices

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

For details, see Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as 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 subject, 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 area, 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.

Methods of measurement

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 subjects 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 12-1 and Table 12-2.

Table 12-1 Response Criteria for Evaluation of Target Lesions

	Evaluation of Target Lesions
Complete response	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	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive disease	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	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 12-2 Response Criteria for Evaluation of Non-target Lesions

	Evaluation of Non-target Lesions
Complete response	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	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Stable disease	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 12-3 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 12-3 Overall Response Status for Subjects 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

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 subject 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 subject 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 subject’ s best response depends on the subsequent assessments. For example, a subject 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 subject lost to follow-up after the first SD assessment would be considered unevaluable.

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 12-4.

Table 12-4 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[a]
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

CR=complete response; NE=non-evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

a 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 B: NCI-CTCAE Grades for Infusion-related Reactions and Skin Toxicities

As indicated in Sections 6.2.4.2 and 6.2.4.3, skin toxicities (rash, xerosis, paronychia, pruritus, fissures and photosensitivity) and infusion-related reactions should be classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, 14 June 2010.

The NCI-CTCAE classification for infusion-related reactions and skin toxicities is summarized in Table 12-5 and Table 12-6 below. A copy of the NCI grading booklet which includes this information will be distributed to all trial sites, and the full classification is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Table 12-5 NCI-CTCAE Classification of Infusion-related Reactions

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, i.v. fluids); prophylactic medications indicated for ≤ 24 hours	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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					

Table 12-6 NCI-CTCAE Classification of Selected Skin Toxicities

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Rash (acneiform)	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	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; limiting instrumental ADL	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	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with i.v. antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Xerosis (Dry skin)	Covering < 10% BSA and no associated erythema or pruritus	Covering 10-30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering > 30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Paronychia	Nail fold edema or erythema; disruption of the cuticle	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	Surgical intervention or i.v. antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation					

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Fissures (Skin and subcutaneous tissue disorders)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: Not applicable					

	CTCAE Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Photosensitivity	Painless erythema and erythema covering < 10% BSA	Tender erythema covering 10-30% BSA	Erythema covering > 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

ADL=activities of daily living; BSA=body surface area; i.v.=intravenous; NSAIDs=nonsteroidal anti-inflammatory drugs.

Appendix C: Management of Skin Toxicities

Section 6.4 and Table 6-6 to Table 6-11 of this protocol provide the specific rules to be followed to manage NCI-CTCAE Grade 1 – 4 Sym004-induced skin toxicities (rash, xerosis, paronychia, pruritus, fissures and photosensitivity).

In addition, this information will be provided to clinical site personnel and trial subjects / carers on pocket-sized, laminated cards.

Copies of the local language version of these cards to be provided here.

Appendix D: Schedule of Assessments

Trial Periods and Assessments	**Screening** Within 14 days prior to Day 1*	**Treatment until Progressive Disease[a]**									**End of Treat-ment Visit[q]**	**End of Trial Interv-ention Visit[s]**	**End of Trial Visit[s]**
Week	**- 2 and -1 IWRS Randomize**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Week Day		**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**			
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Visit Window (Days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**			
Clinical Assessments and Evaluations													
Informed consent	X												
Tumor histology, mutation status, location and extent of disease[b]	X												
Voluntary tumor biopsy (mandatory for dedicated centers)[c]	X												
Blood biomarker Assays[d]	X												
Relevant medical history[e]	X												
Surgical/medical prior treatments for CRC (cytotoxics and biologic targeted agents)	X												
Concomitant medication[f]	X	X			X			X	→	q3w	X	X	
Tumor Assessment[g]	X							X	→	q6w	X		
Vital signs[h] (Arm A+B)	X	X	X	X	X	X	X	X	→	q1w	X	X	
Vital signs[h] (Arm C)	X	X			X			X		q3w	X	X	

Trial Periods and Assessments	**Screening** Within 14 days prior to Day 1*	**Treatment until Progressive Disease[a]**									**End of Treat-ment Visit[q]**	**End of Trial Interv-ention Visit[s]**	**End of Trial Visit[s]**
Week	**- 2 and -1 IWRS Randomize**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Week Day		**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**			
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Visit Window (Days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**			
Physical examination[i] and demographics[j]	X X	X X			X			X	→	q3w	X	X	
ECOG performance status	X	X			X			X	→	q3w	X		
Baseline safety[k]	X												
Adverse events[l]		X	X	X	X	X	X	X	X	q1w	X	X	
Dermatologic assessment Arms A and B	X	X	X	X	X	X	X	X	→	q1w	X		
Dermatologic assessment Arm C	X	X			X			X	→	q3w	X		
12-lead ECG[m]	X	X			X			X	→	q3w	X		
Safety laboratory tests[n]	X	X			X			X	→	q3w	X		
Urine pregnancy test (if applicable)		X			X			X	→	q3w	X		
HIV, HBsAg, HCV Ab	X												
Magnesium level Arms A and B[o]	X	X	X	X	X	X	X	X	→	X	X		
Research Blood Sample[p]: PK study[p1] ADA Assay[p2]	 X X	X	X	 X X		 X X		 X X		 →[p1] →[p2]	 X X		
Quality of life EORTC QLQ-C30 (v3) + EORTC QLQ-CR29		X						X		q6w			

Trial Periods and Assessments	**Screening** Within 14 days prior to Day 1*	**Treatment until Progressive Disease**[a]									**End of Treatment Visit**[q]	**End of Trial Intervention Visit**[s]	**End of Trial Visit**[s]
Week	**- 2 and -1 IWRS Randomize**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Week Day		**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**			
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Visit Window (Days)		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**			
FACT-EGFR 18		X			X			X		q3w			
Sym004 administration Arm A (12 mg/kg/week)		X	X	X	X	X	X	X	X	q1w			
Sym004 administration Arm B (9 mg/kg d1, 6 mg/kg/week thereafter)		X	X	X	X	X	X	X	X	q1w			
Administration of BSC, 5-FU or Capecitabine (Arm C)		according to selected schedule											

*Up to 4 weeks if biopsy taken

a Treatment start is on day of randomization or no later than 72 hours after randomization; Sym004 administration is to continue until PD, excessive toxicity, or withdrawal of consent occurs. After reaching the primary analysis milestone for the trial, the sponsor may reduce study 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.

b Includes primary tumor location, RAS, and BRAF status on archival diagnostic tumor tissue (if available) and histology.

c After all other screening procedures completed and eligibility criteria met: Tumor sample for relevant biomarker assessment including but not limited to RAS status, c-MET, HER2/3, ligands, mandatory biopsies in selected centers with respective commitment.

d After all other screening procedures completed and eligibility criteria met: Blood samples for biomarkers (total volume of 30 mL) including but not limited to RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels.

e Includes relevant prior diseases (see Inclusion/Exclusion Criteria), and treatments for other indications than CRC, administered within 30 days before trial entry.

f Report of concomitant medication within 30 days of trial start, and then q3w based on a continuous assessment; includes prophylactic use of drugs for skin toxicity.

g Baseline CT (or MRI) of the thorax, pelvic region, and abdomen using RECIST v1.1; thereafter q6w from W1D1. Based on clinical need, all results of additional CT (or MRI) done at investigator discretion as standard management will be submitted to study file through end of trial.

h Body temperature, heart rate, blood pressure, after 5 minutes supine at baseline in all subjects; then weekly for Arms A and B and q3w for Arm C.

i Baseline physical examination, including height, weight; thereafter general examination and weight q3w.

j Baseline demographics including age, sex, and ethnicity.

k Baseline, report of all symptoms and persisting toxicities from prior therapy to check compliance with inclusion criteria.

l Per telephone for Arm C.

m Baseline local 12-lead ECG; and q3w in all subjects; results and tracings will be submitted to study file; if weekly magnesium check shows Grade ≥ 3, repeat ECG before drug administration.

n Baseline laboratory studies: hematology (RBC, WBC, neutrophils, platelets, hematocrit, and hemoglobin) and biochemistry (creatinine, creatinine clearance according to Cockcroft-Gault, Na, K, Ca, magnesium, glucose, albumin, ALT, AST, alkaline phosphatase, total bilirubin, CRP, blood urea, INR, aPTT), pregnancy test (if applicable). In all subjects, hematology and biochemistry will be done q3w.

o Weekly magnesium in subjects in Arms A and B; result to be checked by investigator and ECG performed before Sym004 administration in case of Grade ≥ 3; (magnesium q3w in Arm C as part of baseline laboratory studies).

p Includes (1) blood samples for PK study (5 mL/sample; total volume 80 mL) will be obtained from all subjects in Arms A and B at the following time points: Screening, Week 1 Day 1 (30 minutes prior infusion, at end of infusion, 0,5, 1, 2, 4 hours after first infusion), Week 2 Day 1, Week 3 Day 1, Week 5 Day 1, Week 7 Day 1 and end of treatment visit; and (2) blood samples for ADA (5.0 mL/sample; total volume 20 mL) will be obtained from all subjects in Arms A and B at the following time points: Screening, then q2w at Week 3 Day 1, Week 5 Day 1, Week 7 Day 1, then q6w at Week 12 Day 1, Week 18 Day 1, and Week 24 Day 1, and end of treatment visit.

q End of treatment visit is defined as the visit within 5 days after the end of treatment. Subjects who discontinue the treatment due to any reasons other than PD, should continue to attend the tumor assessment visits (q6w) until PD has been observed in addition to the survival follow-up phone/clinic visits.

r End of Trial Intervention Visit: Subjects who have since discontinued treatment without PD, still attending interventional tumor assessment visits q6w, will subsequently attend this visit after assessment of PD, but no earlier than 28 days after stop of treatment. This visit is not applicable if PD is captured at the End of Treatment visit where subjects move directly into the Survival follow-up phase.

s End of Trial Visit: Progressive Disease Follow-up: For subjects who discontinue the trial due to any reasons other than PD, information on the time point of subsequent disease progression (clinical or radiological) must be provided. Survival Follow-up: Subjects discontinuing treatment due to PD or for any other reason will be followed up for survival (e.g., by phone or clinic visits) and information on further antitumor treatments (including treatment in another clinical trial) every 6 weeks (± 1 week) until the end of trial.

Signature Page for VV-CLIN-000344 v1.0

Approval	Meghan Brown Regulatory 25-Oct-2016 19:10:01 GMT+0000

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Approval	Cliff Ding Clinical 26-Oct-2016 14:26:24 GMT+0000

Approval	Ivan Horak Medical 26-Oct-2016 15:45:21 GMT+0000

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Clinical Trial Protocol Amendment

Protocol Amendment No.	4
Scope	Global
Date of Protocol Amendment	25 October 2016
Classification of Amendment	Substantial
Clinical Trial Protocol No.	EMR200637-002 (also designated Sym004-05)
Title	Open-label, Randomized, Controlled, Multicenter Phase II Trial Investigating 2 Sym004 Doses versus Investigator`s Choice (Best Supportive Care, Capecitabine, 5-FU) in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies
Trial Phase	II
IND Number	105953 (previously 119883)
EudraCT Number	2013-003829-29
Coordinating Investigator	Josep Tabernero, MD PhD Head, Medical Oncology Department Vall d'Hebron University Hospital Vall d'Hebron Institute of Oncology (VHIO) P. Vall d'Hebron 119-129 08035 Barcelona SPAIN Tel +34 93 489 4301 Fax +34 93 274 6059 jtabernero@vhio.net
Sponsor	Symphogen A/S Pederstrupvej 93 2750 Ballerup Denmark

	Medical Responsible Dr. Ivan Horak Chief Scientific and Medical Officer Symphogen A/S EU Mobile +45 2055 2604 US Mobile +1 908 938 9313 Email: idh@symphogen.com
Sponsor's Legal Representative (EU)	Symphogen A/S, Pederstrupvej 93, 2750 Ballerup, Denmark
Previous Trial Protocol Version	27 January 2016 / Version 4.0
Current Trial Protocol Version	25 October 2016 / Version 5.0

Previous Protocol Amendments

Amendment no. 1 (Substantial); 20 December 2013 (Global)

Amendment no. 2 (Substantial); 13 March 2015 (Global)

Amendment no. 3 (Substantial); 27 January 2016 (Global)

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the protocol amendment.

See attached electronic signature and date

Name, academic degree	Ivan Horak, MD
Function	Chief Scientific and Medical Officer
Institution	Symphogen A/S
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Coordinating Investigator

I agree to conduct the clinical trial in accordance with this Clinical Trial Protocol and Protocol Amendment and in compliance with Good Clinical Practice and all applicable regulatory requirements.

_____ _____

Signature Date of Signature

Name, academic degree	Josep Tabernero, MD PhD
Function	Head, Medical Oncology Department
Institution	Vall d'Hebron University Hospital Vall d'Hebron Institute of Oncology (VHIO)
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Further Sponsor Responsible Persons

Not applicable.

Principal Investigator Signature

Trial Title	Open-label, Randomized, Controlled, Multicenter Phase II Trial Investigating 2 Sym004 Doses versus Investigator`s Choice (Best Supportive Care, Capecitabine, 5-FU) in Subjects with Metastatic Colorectal Cancer and Acquired Resistance to Anti-EGFR Monoclonal Antibodies
EudraCT Number	2013-003829-29
Protocol Amendment No./Date	4 / 25 October 2016
Corresponding Clinical Trial Protocol Version/Date	5.0 / 25 October 2016
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) (GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some regulatory Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature Date of Signature

Name, academic qualifications

Position (job title)

Address of Institution

Telephone number

Fax number

E-mail address

Table of Contents

1 Introduction

The purpose of this protocol amendment is to:

- Update the text on the biomarkers to be evaluated.
- Clarify reduction of data collection after primary analysis performed.

The changes to be made to the clinical trial protocol and the rationale for the changes are described below.

2 Rationale for Changes

Rationale for Updating the Biomarkers to Be Evaluated

The previous text was revised to ensure that new potential biomarkers could be evaluated as new mutations and technology are identified.

Rationale for Reduction of Data Collection after Primary Analysis Performed

Text was added to clarify the reduction of data collection after primary analysis to collect only relevant information related to safety and efficacy.

3 List of Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold, and deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 4.0, 27 January 2016 (Amendment No. 3)

Change	Section	Page	Previous Wording	New Wording
Addition of secondary protocol number	Cover Page	1	EMR200637-002	EMR200637-002 **(also designated Sym004-05)**
Revise IND number	Cover Page	1	119883	**105953 (previously** 119883**)**
Addition of secondary protocol number	Synopsis	14	EMR200637-002	EMR200637-002 **(also designated Sym004-05)**
Update the secondary endpoints	Synopsis	19	Biomarkers: RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels	Biomarkers: **including but not limited to** RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels
Update the secondary objectives	Section 4.2 Secondary Objectives	27	To identify potential predictive biomarkers of response to treatment (RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands [e.g., amphiregulin, TGF-α, heregulin] plasma protein levels; tumor localization;	To identify potential predictive biomarkers of response to treatment **including but not limited to** RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands [e.g., amphiregulin, TGF-α, heregulin] plasma protein levels; tumor localization;
Update the biomarkers to be evaluated	Section 7.1.1 Screening Period	54	If all eligibility criteria are met and screening procedures are completed: Tumor biopsy (voluntary or mandatory [dedicated centers only] tumor biopsy) - RAS and RAF pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels Blood sampling for biomarker evaluation – RAS pathway mutations, HER2 and MET amplification in circulating DNA (if technically feasible), EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels	If all eligibility criteria are met and screening procedures are completed: Tumor biopsy (voluntary or mandatory [dedicated centers only] tumor biopsy) **including but not limited to** RAS and RAF pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels**;** ~~Blood sampling for~~ **Exploratory** biomarker evaluation **will include but not be limited to the following:** RAS pathway mutations, HER2 and MET amplification in circulating DNA (if technically feasible), EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels**.**

Change	Section	Page	Previous Wording	New Wording
Revise wording for biomarker evaluation	Section 7.6 Biomarkers/ Pharmacogenetics	71	Biomarkers including RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels will be measured.	**Exploratory biomarker evaluation will include but not be limited to the following:** ~~Biomarkers including~~ RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels ~~will be measured~~.
Update the secondary endpoints	Section 8.3.2 Secondary Endpoints	72	Biomarkers RAS pathway mutations, HER2 and MET amplification, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels	Biomarkers **including but not limited to** RAS pathway mutations, HER2 and MET ~~amplification~~ **status**, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α, heregulin) levels
Addition of text for additional biomarker analysis	Section 8.5.2 Analysis of Primary Endpoint(s)	74	Furthermore, subgroup analyses will be performed for subjects with RAS mutations and RAS wild-type, high and low protein expression of HER family ligands, HER2 expression and/or amplification positive and negative, MET expression and/or amplification positive and negative.	Furthermore, subgroup analyses will be performed ~~for~~ **on the basis of subjects' biomarker data, and may include analyses of** subjects with RAS mutations and RAS wild-type, high and low protein expression of HER family ligands, HER2 expression and/or amplification positive and negative, MET expression and/or amplification positive and negative, **and other potential biomarkers.**
Addition of text for additional biomarker analysis	Section 8.5.3 Analysis of Secondary Endpoint(s)	74	Other endpoints (Relative Dose Intensity until PD, Pharmacokinetic Profile, Host immune response: ADA, Biomarkers (MET and HER2 amplification, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α and heregulin) protein expression in blood, RAS pathway mutations, quality of life) will primarily be summarized by use of descriptive statistics, i.e., number of subjects (N), mean, median, standard deviation, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum for continuous variables and counts and percentages for categorical variables.	Other endpoints (Relative Dose Intensity until PD, Pharmacokinetic Profile, Host immune response: ADA, Biomarkers (**including but not limited to** MET and HER2 amplification, EGFR and HER3 ligand (e.g., amphiregulin, TGF-α and heregulin) protein expression in blood, RAS pathway mutations**)**, quality of life) will primarily be summarized by use of descriptive statistics, i.e., number of subjects (N), mean, median, standard deviation, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum for continuous variables and counts and percentages for categorical variables.
Added a section to reduce collection of data after primary analysis	Section 8.7 Data Collection and Analysis Beyond Primary Analysis	76		**After reaching the primary analysis milestone for the trial as defined in section 5.7, the sponsor may reduce study 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.**

Change	Section	Page	Previous Wording	New Wording
Clarify reduction of data collection after primary analysis	Appendix D: Schedule of Assessments	96	Footnote a: Treatment start is on day of randomization or no later than 72 hours after randomization; Sym004 administration is to continue until PD, excessive toxicity, or withdrawal of consent occurs.	Footnote a: Treatment start is on day of randomization or no later than 72 hours after randomization; Sym004 administration is to continue until PD, excessive toxicity, or withdrawal of consent occurs. **After reaching the primary analysis milestone for the trial, the sponsor may reduce study 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.**
Clarify biomarker evaluation	Appendix D: Schedule of Assessments	96	Footnote c: After all other screening procedures completed and eligibility criteria met: Tumor sample for relevant biomarker assessment including RAS status, c-MET, HER2/3, ligands, mandatory biopsies in selected centers with respective commitment.	Footnote c: After all other screening procedures completed and eligibility criteria met: Tumor sample for relevant biomarker assessment including **but not limited to** RAS status, c-MET, HER2/3, ligands, mandatory biopsies in selected centers with respective commitment.
Clarify biomarker evaluation	Appendix D: Schedule of Assessments	96	Footnote d: After all other screening procedures completed and eligibility criteria met: Blood samples for biomarkers (total volume of 30 mL) will include RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels.	Footnote d: After all other screening procedures completed and eligibility criteria met: Blood samples for biomarkers (total volume of 30 mL) ~~will include~~ **including but not limited to** RAS pathway mutations, HER2 and MET status, EGFR and HER3 ligands (e.g., amphiregulin, TGF-α, heregulin) plasma protein levels.

Signature Page for VV-CLIN-000343 v1.0

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Signature Page for VV-CLIN-000343 v1.0