CLINICAL TRIAL PROTOCOL

Trial Title:	A Phase 2, Randomized, Open-Label, Multicenter, Three-Arm Trial of Sym004 versus each of its Component Monoclonal Antibodies, Futuximab and Modotuximab, in Patients with Chemotherapy-Refractory Metastatic Colorectal Carcinoma and Acquired Resistance to Anti-EGFR Monoclonal Antibody Therapy
Short Title:	Sym004 versus Futuximab or Modotuximab in Patients with mCRC
Sponsor:	Symphogen A/S [redacted]
Sponsor's Medical Expert:	[redacted]
Coordinating Investigator:	[redacted]
Trial ID:	Sym004-13
Trial Phase:	Phase 2
IND Number:	105953
EudraCT Number:	2018-000618-39
Protocol Version/Date:	6.0 / 18-Jan-2019 (Amendment 5)
Previous Protocol Versions/Dates:	5.0 / 02-Aug-2018 (Amendment 4) 4.0 / 08-May-2018 (Amendment 3) 3.0 / 08-Mar-2018 (Amendment 2) 2.0 / 02-Jan-2018 (Amendment 1) 1.0 / 27-Oct-2017

Sponsor Declarations

The trial will be conducted in compliance with this clinical trial protocol, International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6(R2): Guideline for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and applicable regulations.

The Sponsor has appointed a Coordinating Investigator for the trial. This Coordinating Investigator will provide input to the trial design and act as overall coordinator for Investigators across all sites. The Coordinating Investigator will furthermore sign off the Clinical Trial Report (CTR) on behalf of all Investigators.

Lists of Investigators responsible for conducting the trial, medically qualified physicians responsible for all site-related medical decisions (if other than the Investigators), monitors, clinical laboratories, and other medical and/or technical departments and/or institutions involved in the trial are provided as separate documents.

Principal Investigator Signature Page

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

- To assume responsibility for the proper conduct of the clinical trial at this Investigational Site
- Not to implement any changes to the clinical trial protocol without agreement from the Sponsor and prior review and written approval from the appropriate Health Authority (as indicated) and the Institutional Review Board/ Ethics Committee, except where necessary to eliminate an immediate hazard to the patients
- That I am aware of, and will comply with "Good Clinical Practice" (ICH E6(R2) GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and all applicable regulatory requirements
- That all site staff to which I have delegated tasks for this clinical trial, are appropriately selected and adequately informed about the investigational product(s) and of their trial-related duties and functions as described in the clinical trial protocol

_____ _____
Signature Date of Signature

Name: _____

Academic Degree: _____

Function: _____

Institution: _____

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LIST OF ABBREVIATIONS AND EXPANDED TERMS

Abbreviation	Expanded Term
1M FUP	1-Month Follow-up
4.5/3 mg/kg	4.5 mg/kg loading dose followed by weekly doses of 3 mg/kg of Futuximab or Modotuximab
5-FU	5-Fluorouracil
9/6 mg/kg	9 mg/kg loading dose followed by weekly doses of 6 mg/kg of Sym004
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AT	As-Treated (population)
AUC	Area Under the Concentration-Time Curve
β-hCG	Beta-Human Chorionic Gonadotropin
BSC	Best Supportive Care
C	Cycle
C#D#	Cycle Number (#) Day Number (#)
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
C_{EOI}	Concentration at the End of Infusion
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Concentration
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Carcinoma
Cr_{Cl}	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography

Abbreviation	Expanded Term
CTCAE v5	Common Terminology Criteria for Adverse Events (Version 5)
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTR	Clinical Trial Report
C_{trough}	Trough Concentration
dMMR	Mismatch Repair-Deficient
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECD	Extracellular Domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EOC#	End of Cycle Number (#)
EOI	End of Infusion
EOT	End of Treatment
FDA	Food and Drug Administration
FOLFIRI	5-fluorouracil, folinic acid, and irinotecan
FOLFOX	5-fluorouracil, folinic acid, and oxaliplatin
FSH	Follicle-Stimulating Hormone
FUP	Follow-up
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IC	Investigator's Choice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgG1	Immunoglobulin G1
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio

Abbreviation	Expanded Term
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IV	Intravenous
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
mAb	Monoclonal Antibody
MAF	Mutation Allele Frequency
mCRC	Metastatic Colorectal Carcinoma
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability-High
NE	Not Evaluable
NRAS	Neuroblastoma *RAS* Viral Oncogene Homolog
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death-Ligand 1
PE	Pulmonary Embolism
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PR Interval	ECG interval between beginning of the P-wave to beginning of the QRS complex
PS	Performance Status
PSA	Prostate Specific Antigen
Q#M	Every Number (#) Months
Q#W	Every Number (#) Weeks
Q1W	Once weekly
QT Interval	ECG interval between onset of QRS complex to end of the T-wave
QTc Interval	QT interval corrected for heart rate
RAS	Rat Sarcoma
RBC	Red Blood Cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (Version 1.1)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Expanded Term
SAR	Suspected Adverse Reaction
SD	Stable Disease
SOI	Start of Infusion
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Serum Elimination Half-Life
TAS-102	Trifluridine/Tipiracil
TdP	Torsade de Pointes
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TN	Triple Negative (mCRC)
ULN	Upper Limit of Normal
U.S.	United States
UV	Ultraviolet
V_d	Volume of Distribution
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WNL	Within Normal Limits
WOCBP	Woman of Childbearing Potential
WT	Wild-Type

1 SYNOPSIS

CLINICAL TRIAL PROTOCOL	
Trial Title	A Phase 2, Randomized, Open-Label, Multicenter, Three-Arm Trial of Sym004 versus each of its Component Monoclonal Antibodies, Futuximab and Modotuximab, in Patients with Chemotherapy-Refractory Metastatic Colorectal Carcinoma and Acquired Resistance to Anti-EGFR Monoclonal Antibody Therapy
Trial ID	Sym004-13
Trial Phase	Phase 2
INVESTIGATIONAL MEDICINAL PRODUCTS	
Investigational Medicinal Products	Sym004 is a mixture of 2 recombinant, human-mouse chimeric, immunoglobulin G1 (IgG1) monoclonal antibodies (mAbs) (futuximab and modotuximab) targeting 2 non-overlapping epitopes of the Epidermal Growth Factor Receptor (EGFR). The Investigational Medicinal Products (IMPs) in this trial are Sym004 (a mixture of futuximab and modotuximab), the drug product futuximab, and the drug product modotuximab. **Supplies** Labeled IMP supplies will be provided by the Sponsor as liquid formulations for intravenous (IV) infusion. Sym004: Single-use clear glass vials contain: • A nominal fill volume of 20 mL • At a concentration of 25 mg/mL for a total vial content of 500 mg Futuximab: Single-use clear glass vials contain: • A nominal fill volume of 10 mL • At a concentration of 25 mg/mL for a total vial content of 250 mg Modotuximab: Single-use clear glass vials contain: • A nominal fill volume of 10 mL • At a concentration of 25 mg/mL for a total vial content of 250 mg
TRIAL OBJECTIVES	
Primary Objective	**As of Amendment 5:** Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as detailed below are no longer applicable. Only clinical safety-related evaluations will be conducted. To evaluate the relative contribution of futuximab and modotuximab to the antitumor activity of Sym004 following 8 weeks of treatment in genomically-selected patients with chemotherapy refractory metastatic colorectal carcinoma (mCRC) and acquired resistance to anti-EGFR mAb therapy. Note: Antitumor activity will be assessed by changes in tumor measurements (as determined according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]).
Secondary Objective	To evaluate the safety profile of a weekly dosing regimen of Sym004 versus single agent futuximab or single agent modotuximab.
Exploratory Objective	To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood, skin biopsies, and tumor biopsies to be collected). Tumor biopsies will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models.*
TRIAL DESIGN	
Design Summary	**As of Amendment 5:** This amendment to the clinical trial protocol is based on the Sponsor's decision to discontinue the trial for administrative reasons, effective 20Dec2018; the intent to discontinue the trial was communicated to all active sites on this date. As a result, the original trial design as described below is no longer applicable, future accrual has been halted, and a reduction in the scope of non-safety-related assessments being conducted under this protocol has been implemented.

	Patients consented as of the trial discontinuation date, and determined to meet study eligibility criteria, may be treated with IMP and may continue therapy until the occurrence of one of the following: unacceptable toxicity or other conditions preventing further administration, documented progressive disease (PD), or the patient's decision to withdraw. Treated patients will be followed and assessed for only clinical safety-related concerns throughout their treatment period and at minimum for 30 days after the last administration of IMP. **The pre-Amendment 5 trial design was as follows**: This is a Phase 2, open-label, three-Arm trial with randomization in the ratio of 1:1:1 to either Sym004 (Arm A) versus futuximab (Arm B) or modotuximab (Arm C) in genomically-selected patients with chemotherapy-refractory mCRC and acquired resistance to anti-EGFR mAb therapy. The study is designed to evaluate the relative antitumor activity of each agent as assessed by imaging studies performed after 8 weeks of treatment (i.e., at the end of Cycle 2 [EOC2]). Following consent and prior to randomization, genomic analysis of *RAS*, *BRAF* V600, and *EGFR*-ECD mutation status will be conducted on blood samples obtained from each potential patient. Triple-negative (TN) results as defined in trial eligibility criteria will be required for initial eligibility. Patients with TNmCRC will continue in the screening process. Once deemed fully eligible, patients will be randomized to Arm A, Arm B, or Arm C. • Patients randomized to Arm A will receive Sym004 by the IV route, at a loading dose of 9 mg/kg on Cycle 1 Day 1 (C1D1) followed by weekly doses of 6 mg/kg beginning on C1D8 (total of 4 doses per 28-day cycle). • Patients randomized to Arm B or Arm C will receive futuximab or modotuximab, respectively, by the IV route, at a loading dose of 4.5 mg/kg on C1D1 followed by weekly doses of 3 mg/kg beginning on C1D8 (total of 4 doses per 28-day cycle). Dosing cycles of 28 days (± 2 days) will continue until documented disease progression or another criterion for discontinuation is met. Antitumor activity will be assessed at the end of every 2 cycles (every 8 weeks [Q8W]). At the EOC2 tumor assessment: • Patients assigned to Arm A (Sym004) with a documented objective response (OR) or Stable Disease (SD) will continue to receive Sym004; patients with documented progressive disease (PD) at the EOC2 will be discontinued from study • Patients assigned to Arm B (futuximab) or Arm C (modotuximab) with a documented OR or SD will be crossed-over to receive Sym004; patients with documented PD at the EOC2 (or prior to the EOC2) will be offered the opportunity to crossover to receive Sym004 or will be discontinued from study To be considered evaluable for antitumor activity assessment, patients must have completed 2 cycles of dosing inclusive of EOC2 disease imaging studies (i.e., computed tomography [CT]/magnetic resonance imaging [MRI]) and must have received any amount of their assigned IMP during that period, or have PD documented by imaging studies prior to the EOC2. Non-evaluable patients and patients discontinuing from study prior to the EOC2 for reasons other than documented PD will not be replaced *(every effort will be made to obtain imaging studies at the time of discontinuation).* Site Investigators will evaluate patients for eligibility and submit relevant information. Designated Eligibility Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization. Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigator(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns.
PATIENT SELECTION	
Investigational Sites	**As of Amendment 5:** As of the trial discontinuation date (20Dec2018), a single center in the United States had consented and screened patients. Two (2) of 5 patients screened were determined to be eligible for participation

	and both were enrolled in the study. The total number of sites planned will not be participating. This is a multicenter, multinational trial • Number of Sites: Approximately 20 sites may participate based on anticipated accrual • Number of Countries: Approximately 4-6 countries in North America and Europe
Planned Sample Size	**As of Amendment 5**: Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients planned will not be enrolled. Up to approximately 54 evaluable patients (18 evaluable patients per Arm)
Key Eligibility Criteria	**As of Amendment 5**: Effective 20Dec2018, accrual to this trial has been halted; however, patients consented prior to the effective date will be required to meet the following eligibility criteria: **Patients to be Included** *(patients must meet all the following criteria)* 1. Male or female patients, ≥ 18 years 2. Patients with histologically- or cytologically-confirmed mCRC 3. Patients with microsatellite instability-high (MSI-H) / mismatch repair-deficient (dMMR) tumors must have received prior therapy with pembrolizumab, nivolumab, or other programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway blocker, and must have progressed on that therapy. 4. Patients meeting the protocol definition of TNmCRC assessed in the screening blood test (ctDNA): a. Without *RAS* (*KRAS* and *NRAS*) MAF ≥ 20% for mutations in the following codons: o Exon 2: codon 12, 13 o Exon 3: codon 59, 61 o Exon 4: codon 117, 146 b. Without *BRAF* V600E mutation at any mutation allele frequency (MAF) c. Without *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations at any MAF Note: Centralized genomic analysis to be performed; peripheral blood to be collected for assessment of circulating tumor DNA (ctDNA) by *Guardant360*®. 5. Patients with mCRC currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor 6. Patients with measurable disease according to RECIST v1.1, and willingness to undergo a total of 2 biopsies of a primary or metastatic tumor site(s) considered safely accessible for biopsy 7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed (includes intolerance to) those regimens. Prior standard chemotherapy may not have included TAS-102 or regorafenib but must have included all the following agents (where approved in the country). a. Fluoropyrimidines, irinotecan, oxaliplatin b. An anti-vascular endothelial growth factor (VEGF) pathway inhibitor approved for treatment of mCRC c. At least one anti-EGFR mAb approved for the treatment of mCRC Note: Patients who have withdrawn from standard therapy(ies) due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will be eligible to enter the study Patients who received adjuvant chemotherapy and had documented recurrence (by imaging studies) during or within 6 calendar months of completion of the adjuvant chemotherapy are permitted to count the adjuvant therapy as one regimen of chemotherapy 8. Patients with "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC must have: a. Received treatment with an anti-EGFR for ≥16 weeks b. PD documented by imaging or clinical findings ≤ 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 treatment to date of consent for this trial (regardless of the line of therapy in which it was used)

	9. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 10. Patients who are either not of childbearing potential or who agree to use a highly effective method of contraception. 11. Patients with the ability to understand and give written informed consent **Patients to be Excluded** *(patients must not meet any of the following criteria* 1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 3 months after the last dose of IMP. 2. Patients with a prior history of any of the following mutations in their tumor at the time of any previous assessment: a. *RAS* (*KRAS* and *NRAS*) mutations in the following codons: o Exon 2: codon 12, 13 o Exon 3: codon 59, 61 o Exon 4: codon 117, 146 b. *BRAF* V600E mutation c. *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations 3. Patients with known, untreated central nervous system (CNS) or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required 4. Patients with an active second malignancy or history of another malignancy within the last 5 years (see protocol for exceptions) 5. Patients with any of the following hematologic abnormalities at baseline: a. Hemoglobin < 9 g/dL b. Absolute neutrophil count (ANC) < 1,500 per mm^3 c. Platelet count < 100,000 per mm^3 6. Patients with any of the following serum chemistry abnormalities at baseline: a. Total bilirubin > 2.0 × the upper limit of normal (ULN) for the institution b. Alkaline phosphatase (ALP) > 2.5 × the ULN for the institution (> 5 × ULN if due to hepatic involvement by tumor) c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × the ULN for the institution (> 5 × ULN if due to hepatic involvement by tumor) d. Creatinine clearance [Cr_{Cl}] < 30 mL/min as calculated by the Cockroft-Gault formula e. Magnesium < 1.2 mg/dL 7. Patients with: a. Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 4 weeks prior to first administration of IMP unless adequately treated and considered by the Investigator to be stable b. Active uncontrolled bleeding or a known bleeding diathesis 8. Patients with a known clinically significant cardiovascular disease or condition, as specified in the protocol 9. Patients with non-healing wounds on any part of the body 10. Patients with significant gastrointestinal abnormality, including: a. Diarrhea > Grade 1 at the time of randomization b. Requirement for IV alimentation 11. Patients with skin rash > Grade 1 from prior anti-EGFR therapy at the time of randomization 12. Patients with any unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, peripheral neuropathy, and/or end-organ failure being adequately managed by hormone replacement therapy 13. Patients with a known or suspected hypersensitivity to any of the excipients of formulated IMP(s) **Drugs and Other Treatments to be Excluded** *(patients must not be receiving any of the following)* 1. Prior treatment with TAS-102 or regorafenib

	2. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks prior to first administration of IMP and during study, with exceptions as specified in the protocol: 3. Any other investigational treatments within 4 weeks prior to and during study; includes participation in any medical device or other therapeutic intervention clinical trials 4. Radiotherapy: a. For lesions to be used as target lesions, within 4 weeks prior to first administration of IMP unless disease progression has been documented in the lesion post-radiotherapy, and during study b. For non-target lesions within 1 week prior to first administration of IMP 5. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to first administration of IMP and during study; allowed therapies are specified in the protocol.
EXPERIMENTAL PLAN	
Randomization	**As of Amendment 5:** As of the trial discontinuation date (20Dec2018), 5 patients had provided written consent for trial participation; following screening, 2 were determined to be eligible. The first patient was deemed eligible prior to the trial discontinuation date and was randomized to Arm B (futuximab). The second patient was deemed eligible after the trial discontinuation date and although randomized to Arm B (futuximab), per Sponsor decision was enrolled to Arm A to receive Sym004. The pre-Amendment 5 randomization plan detailed below will not be followed. Randomization to Arm A (Sym004) versus Arm B (futuximab) or Arm C (modotuximab) will take place once a consented patient has completed all the necessary Screening procedures (within the 14-day screening window) and is authorized as eligible for study entry. C1D1 dosing is to occur on the day of randomization or within 3 days (72 hours) after randomization.
IMP ADMINISTRATION	
Doses to be Administered	**As of Amendment 5:** Two (2) patients screened and determined to be eligible have been treated with IMP. The first patient deemed eligible prior to the trial discontinuation date (20Dec2018) was randomized to Arm B (futuximab) and crossed over to Arm A (Sym004) at the EOC1 per Sponsor decision; the second patient deemed eligible after the trial discontinuation date was randomized to Arm B (futuximab), however per Sponsor decision was enrolled to Arm A to receive Sym004. With this amendment, the doses of IMP to be delivered remain unchanged; however, the pre-Amendment 5 crossover dose plan as detailed below is no longer in effect. **Sym004** • Loading dose of 9 mg/kg on C1D1 • Thereafter, weekly doses (± 2 days) of 6 mg/kg, beginning on C1D8 **Futuximab and modotuximab, each** • Loading dose of 4.5 mg/kg on C1D1 • Thereafter, weekly doses (± 2 days) of 3 mg/kg, beginning on C1D8 **Changes in Dose to be Administered** Each patient will continue to be treated with IMP at that same dose level, unless dose reduction is necessary due to the occurrence of an adverse event(s) (AEs) warranting such action. **Crossover Dose of Sym004** At the EOC2, ongoing patients from Arm B and Arm C will be crossed-over from futuximab or modotuximab to Sym004; crossover may occur prior to the EOC2 in the event of early radiographic documentation of PD Upon crossover, Sym004 will be administered at the dose level that contains the corresponding dose level of the individual antibody futuximab or modotuximab as was previously being administered (prior to crossover). Therefore, patients receiving futuximab or modotuximab at the dose of 3 mg/kg or the reduced dose of 1.5 mg/kg will crossover to receive Sym004 at the dose of 6 or 3 mg/kg, respectively.

	Sym004 treatment may be initiated at least one week after the latest dose of futuximab or modotuximab, unless AEs prevent this according to the protocol retreatment criteria. Dosing of Sym004 may continue until further PD is observed
Route of Administration	IV infusions via central or peripheral indwelling venous access catheter, utilizing a controlled infusion device
Infusion Materials	Infusion set containing a 0.22 micron in-line filter
Infusion Volume	**Arm A** (9/6 mg/kg) • 500 mL for 9 mg/kg infusions • 250 mL for ≤ 6 mg/kg infusions **Arm B and Arm C** (4.5/3 mg/kg) • 500 ml for 4.5 mg/kg infusions • 250 ml for ≤ 3 mg/kg infusions
Diluent and Delivery	Commercially available sterile 0.9 % Sodium Chloride Injection, USP or local equivalent solution for IV infusion
Infusion Duration	**Arm A** • Initial infusion (9 mg/kg in 500 mL) to be administered over 1 hour (+10 min). The maximum infusion rate of 500 mL/hour should not be exceeded throughout administration. • Subsequent infusions (≤ 6 mg/kg in 250 mL) to be delivered over 30 minutes (+ 10 min), with a maximum infusion rate of 500 mL/hour. **Arm B and Arm C** • Initial infusion (4.5 mg/kg in 500 mL) to be administered over 1 hour (+10 min). The maximum infusion rate of 500 mL/hour should not be exceeded throughout administration. • Subsequent infusions (≤ 3 mg/kg in 250 mL) may be delivered over 30 minutes (+10 min), with a maximum infusion rate of 500 mL/hour.
Schedule	Once weekly (± 2 days) on Day 1, 8, 15, and 22 of each 28-day cycle (4 weeks [28 days] equals 1 dosing cycle).
Observation Requirements	Patients will be treated and followed on an outpatient basis. All patients: • Will be observed for a minimum of 2 hours following completion of the first administration of IMP on C1D1 and a minimum of 1 hour following completion of subsequent infusions of IMP (C1D8 and thereafter). • 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.
Premedication	**Premedication for Infusion-Related Reactions (IRRs)** Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP. All patients will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen. Recommended premedication doses are provided. **Premedication for Dermatologic AEs** To minimize the risk of dermatologic AEs, all patients will receive at minimum during Cycle 1 and 2 minocycline or doxycycline, and will apply topical therapy to the face and chest with a low potency steroid cream, and moisturizing creams/ointments to the hands and body. Use of fragrance-free soaps will be encouraged throughout the treatment period.
CONTINUED TREATMENT	
Continued Treatment	Upon completion of Cycle 1, in the absence of unacceptable toxicity or documented PD, patients may continue to receive additional cycles of IMP provided protocol-specified retreatment guidelines are met.
Cycle 2	Administration will be at the same dose (unless dose reduction is necessary) and infusion duration established for the patient during the previous cycle, and on the same weekly schedule.

Treatment after Cycle 2	**As of Amendment 5**: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion. Enrolled patients (2 total) have been either crossed over to receive or are receiving Sym004, and may continue to receive Sym004 until confirmation of PD. The pre-Amendment 5 plan for continued treatment after Cycle 2 as detailed below will not be followed. Disease assessment and tumor measurements will be conducted at the EOC2. Patients in Arm A, in the absence of PD, may continue to receive additional cycles of Sym004. Patients in Arm B or Arm C, in the absence of PD, will be crossed-over to receive Sym004; patients with PD will be offered the opportunity to crossover to receive Sym004 (until further PD is observed).
TOXICITY MANAGEMENT	
AE Management	**Dose Delay** AEs that do not meet the protocol discontinuation criteria, but nevertheless warrant dose modification, may be managed by temporary dose delay to allow for amelioration of the toxicity. **Dose Reduction** In the event of Grade 3 treatment-related AEs that are self-limiting or can be managed by supportive care or other therapy, the patient may continue in the study if there is evidence of response, disease stabilization, or other clinical benefit, but must do so at a reduced dose of IMP. Patients may not be retreated until retreatment criteria are met. Once a patient has undergone dose reduction for any reason, the patient will continue to be treated at the reduced dose throughout the remainder of their time on study treatment.
Infusion-Related Reactions	Instructions for the grading and management of IRRs are provided. In all cases the Investigator should use best clinical judgment in managing such reactions. • For Grade 3 reactions, the infusion will be STOPPED. The patient will be either discontinued from treatment or must receive subsequent treatments at a reduced dose and at a prolonged infusion rate. • For Grade 4 reactions, the infusion will be STOPPED and the patient will be permanently discontinued from treatment.
Dermatologic Toxicity	Patients will be monitored weekly for evidence of dermatologic AEs. Dose delay and/or intrapatient dose-reduction(s) will be required upon occurrence of Grade 3 AEs, and may be implemented in the event of a Grade 2 dermatologic reaction that is debilitating for the patient. Recommendations for management of Grade 1 to 3 dermatologic AEs are provided. Patients must be withdrawn from IMP treatment in the event of a Grade 4 dermatologic AE.
Hypomagnesemia, Hypocalcemia, and Hypokalemia	Patients will be monitored weekly for hypomagnesemia, hypocalcemia, and hypokalemia. In the event of Grade 3-4 hypomagnesemia, repletion is required as well as predosing electrocardiograms (ECGs) to monitor for QTc prolongation. For Grade 4 hypomagnesemia that is refractory to IV magnesium-replacement therapy, dosing with Sym004 should be delayed or reduced. Full management instructions are provided in the protocol.
SAFETY MONITORING	
AE Grading	For reported AEs, the Common Terminology Criteria for Adverse Events (Version 5) (CTCAE v5), will be used to grade the severity of the AE.
Safety Reporting	Clinical and laboratory safety data will be reviewed on an ongoing basis to make decisions regarding the advisability of continuing accrual. To facilitate this, the following will be promptly reported to the Sponsor or designee: • Serious adverse event(s) (SAE)s, within 24 hours of Investigator awareness • AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to study drug • IRRs (≥ Grade 3)
Safety Monitoring	Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigators(s) and the

	Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns.
STUDY ASSESSMENTS	
Efficacy Assessment	**As of Amendment 5**: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion until confirmation of PD. The pre-Amendment 5 disease status assessment schedule as detailed below will not be followed. **Disease Status** (Local Assessment) • Diagnostic imaging (CT/MRI) for tumor assessment; EOC2 and every 8 weeks thereafter (Q8W) • Tumor assessment (per RECIST v1.1) for determination of antitumor activity (OR, SD)
Safety Assessments	**Safety Assessments** Patients to be monitored throughout the treatment and follow-up periods for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, physical findings including dermatologic changes, vital signs (VS), laboratory data, and ECGs.
ADA, PK, Genomic, and Pharmacodynamic Assessments	**As of Amendment 5:** Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related evaluations will be conducted. ADA and samples for exploratory PK and PD assessments (in peripheral blood, skin biopsies, and tumor biopsies) will not be collected. Genomic samples for eligibility assessment were obtained at prescreening and analyzed; however post-dosing genomic samples will not be collected. **The pre-Amendment 5 specialty assessment plan was as follows**: • **Immunogenicity** (Specialty Lab) Serum sampling to assess the potential for anti-drug antibody (ADA) formation. • **Exploratory Pharmacokinetics** (Specialty Lab) Serum sampling to support determination of the AUC_{inf}, $AUC_{0\text{-}168h}$, $T_{½}$, CL, CL_{ss}, V_d, C_{trough} (start of infusion [SOI]) and C_{max} (end of infusion [EOI]) concentrations. Data will also enable population pharmacokinetic (PK) modeling for further PK characterization. • **Genomic Analyses** (Specialty Lab) Peripheral blood sampling for ctDNA bioanalyses • **Pharmacodynamic Analyses** (Specialty Lab) Peripheral blood, skin biopsies, and tumor biopsies for potential predictive and/or prognostic biomarker assessment
DISCONTINUATION AND FOLLOW-UP	
Key Treatment Discontinuation Criteria	Patients are to be discontinued from treatment in the event of any of the following: 1. PD: Confirmed radiologically (and evaluated according to RECIST v1.1) *(patients receiving futuximab or modotuximab may opt to crossover and receive Sym004)* 2. Clinical Progression: Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation *(patients receiving futuximab or modotuximab may opt to crossover and receive Sym004)* 3. AEs, including: • Hepatotoxicity characterized by Hy's Law criteria (see protocol) • Any of the following AEs: o Need for more than 2 dose reductions (Arm A), or more than 1 dose reduction (Arm B or Arm C) o Grade 4 IRR o Grade 4 EGFR-associated dermatologic AE o Torsade de pointes arrhythmia or other life-threatening arrhythmias • Any other AE or SAE considered by the Investigator to require treatment discontinuation 4. Physician Decision
Replacements	After randomization to the study, no patients will be replaced. Patients not evaluable (NE) for antitumor activity assessment, as defined, or patients discontinuing from study prior to the EOC2 due

	to either documented PD or for reasons other than documented PD, will not be replaced.
Follow-up	All follow-up (FUP) visits and assessments, as described, should be conducted to the fullest extent possible. • End of Treatment (EOT) evaluations to be conducted within ~ 7 to 10 days following the decision to discontinue the patient from treatment • 1 Month FUP evaluations to be conducted ~ 30 days (+ 7 days) following the last dose of IMP • Long-Term FUP for Safety: If an observed toxicity thought to be related to IMP has not resolved by the 1M FUP evaluation, an additional follow-up AE assessment will be conducted, if feasible, to confirm that the event has either resolved, returned to baseline status, or been adequately explained.* **Documentation may be obtained by telephone, e-mail, or submitted in writing. An in-person visit will not be required.*
ANALYSIS PLAN	
Statistical Methods	**As of Amendment 5:** Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. Planned efficacy analyses as detailed below will not be performed. **Analysis Sets** • As-Treated (AT) Analysis Set: This analysis set includes all patients who took part of any dose of study treatment, will be used as basis for the evaluation of antitumor effects and safety analyses. All analyses using this population will be based on the treatment actually received. • PK Analysis Set*: All patients in the AT analysis set who receive any amount of their assigned dose of the IMPs (i.e., Sym004, futuximab, or modotuximab), and have a measurable concentration of at least one of the IMPs for at least one timepoint after the first dose, with no significant protocol deviations that may impact the data. ***As of Amendment 5**: PK analysis will not be performed, therefore the PK analysis set is no longer applicable. **Primary Efficacy Analysis** Percentage change from baseline in the sum of the diameter of tumors designated as target lesions (per RECIST v1.1), as documented at the EOC2 tumor assessment will be calculated and plotted by treatment Arm using Waterfall plots. Percent of patients with on-study tumor shrinkage will be presented along with the associated 95% confidence intervals (CI). Magnitude of tumor shrinkage will also be summarized by treatment Arm, as appropriate. **Safety Analyses** The safety evaluations will focus on AEs and laboratory assessments. All patients included in the AT analysis set will be evaluated by treatment Arm in the safety analysis. Special attention will be paid to dermatologic toxicities, hypomagnesemia, hypocalcemia, hypokalemia, and IRRs.
Sample Size Considerations	**As of Amendment 5:** Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients will not be enrolled. Two (2) patients consented prior to the trial discontinuation date and subsequently determined to be eligible have been entered to the study. The pre-Amendment 5 sample size considerations detailed below are no longer valid. Based on the results of Phase 1 and Phase 2 studies, 37% to 40% of patients receiving Sym004 9/6 mg/kg weekly treatment are expected to have tumor shrinkage at Week 8. With no knowledge of the anti-cancer effect of futuximab and modotuximab, up to 18 patients per Arm may be enrolled and treated to differentiate the rates of 35% versus 10% using a Simon's 2-stage Minimax design, with a 5% significance level and 80% power for each of the futuximab and modotuximab Arms. In Stage 1, 11 patients will be enrolled in each Arm and treated. If no more than 1 patient has tumor shrinkage in an Arm, further enrollment will be stopped in that Arm. Otherwise, an additional 7 patients will be enrolled in Stage 2. A contemporary reference Sym004 Arm will be included in the study to ensure the interpretability of tumor shrinkage data for futuximab and modotuximab. If either of the futuximab or modotuximab Arms continues in Stage 2 or beyond, the Sym004 Arm enrollment will continue.

Interim Analysis	**As of Amendment 5:** Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned interim analyses as described below will not be performed. Tumor shrinkage will be evaluated at the end of Stage 1 and Stage 2. No other interim analysis is planned.
TRIAL REPORTING	
Final Clinical Trial Report (CTR)	**As of Amendment 5:** Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as previously described are no longer applicable. Only clinical safety-related evaluations will be conducted. An abbreviated CTR will be prepared upon completion of the trial rather than the full integrated report described below. Final integrated clinical/statistical trial report will be prepared upon reaching the predefined data cut-off for primary analysis (all patients complete their first on-study tumor assessment).

2 SCIENTIFIC BACKGROUND AND RATIONALE

2.1 Background

2.1.1 Metastatic Colorectal Carcinoma

In 2012, the worldwide incidence of colorectal carcinoma (CRC) was estimated to be over 1.36 million (1). Curative surgical treatment is only possible in the early stages of the disease (Stage I/II) and if the malignancy has not spread beyond the regional lymph nodes (Stage III). Five-year survival for patients with Stage I CRC is approximately 90%. Survival decreases with increasing stage of disease and the five-year survival of patients with Stage IV CRC, the patient population targeted in this trial, diminishes to approximately 12% (2).

2.1.2 Current Treatment of Metastatic Colorectal Carcinoma

Over the last 20 years, therapy for metastatic CRC (mCRC) has evolved rapidly with the approval of multiple new therapeutic agents as well as the development of combination regimens that have resulted in improved survival for patients with this malignancy. Novel chemotherapeutics approved during this period include irinotecan, oxaliplatin, and the fluoropyrimidine, capecitabine (2-8). More recently two additional orally administered agents, the tyrosine kinase inhibitor (TKI) regorafenib (9, 10) and the combination of trifluridine and tipiracil (TAS-102) (11) have been approved for third- and fourth-line therapy of mCRC. Targeted therapies that have been introduced include: (a) immune checkpoint blockers (pembrolizumab, nivolumab) in a population of CRC patients with a high level of microsatellite instability (MSI-H) due to defects in DNA mismatch repair (mismatch repair-deficient [dMMR]) (12-14); (b) inhibitors of angiogenesis (bevacizumab, ziv-aflibercept, and ramucirumab), (6-8, 10, 15) and (c) anti-epidermal growth factor (EGFR) monoclonal antibodies (mAbs) (cetuximab and panitumumab) (2-8, 16-20).

2.1.2.1 Therapy with anti-EGFR Monoclonal Antibodies

Metastatic CRC (mCRC) is treated with a variety of regimens of combination chemotherapy and targeted agents, including mAbs targeting the epidermal growth factor receptor (EGFR). The approved anti-EGFR antibodies, cetuximab and panitumumab, have been shown to be active in first-, second-, and third-line therapy of CRC (2-8, 16-20). Cetuximab and panitumumab have been shown to have single agent activity (6-9), and to increase the effectiveness of regimens including both 5-fluorouracil (5-FU), folinic acid, and irinotecan (e.g., FOLFIRI) as well as 5-FU, folinic acid, and oxaliplatin (FOLFOX) in the first- and second-line treatment of mCRC (2-8, 16-20).

2.1.2.2 Resistance to Anti-EGFR Antibodies

Despite the clearly documented activity of anti-EGFR antibodies, only approximately 10% of naïve patients respond to these agents while many mCRC patients are refractory prior to beginning therapy (innate resistance), and patients who initially respond ultimately progress while on therapy (acquired resistance). Subsequent studies have documented that a variety of factors impact prognosis or are responsible for primary and acquired resistance, and have documented the evolution of changes in patients treated with anti-EGFR mAbs (21-24).

RAS Mutations

Analysis of tumor genomic data first documented that efficacy was only demonstrable in patients whose CRC expressed the wild-type (WT) Kirsten Rat Sarcoma (*KRAS*) viral oncogene homolog genotype, but subsequent studies and analyses extended these findings of resistance to therapy to patients with evidence of specific mutations in either *KRAS*, exon 2, 3 and 4, or neuroblastoma rat sarcoma (*NRAS*) viral oncogene homolog, exon 2, 3 and 4 (25, 26). Patients with documented *RAS* mutations not only do not respond to treatment (25-28) with anti-EGFR antibodies but administration of these mAbs appears to have a deleterious effect in this population (6). The *KRAS/NRAS* mutations occur in approximately 50% of treatment-naïve CRC patients (29).

BRAF mutation

BRAF mutations occur in approximately 8% to12% of patients with CRC, are found primarily in right-sided colonic tumors, and have been well-established as a negative prognostic factor (3, 25-28, 30-34). A specific mutation of the *BRAF* gene at amino-acid position 600 (*BRAF* V600E) has been documented to be associated with poor prognosis in patients with CRC, including patients receiving treatment with anti-EGFR mAbs. In addition to the well-documented prognostic effects of the *BRAF* V600E mutation, increasing evidence has accumulated supporting that the presence of this mutation in patients with *RAS* WT CRC, detected in tumor tissue or blood as assessed by circulating tumor deoxyribonucleic acid DNA (ctDNA), is also associated with lack of response to anti-EGFR mAbs (35-43).

EGFR-ECD Mutations

Mutations in *EGFR*-extracellular domain (ECD) are a recently discovered mechanism of acquired resistance in a subset of patients with mCRC who have responded to and progressed after treatment with the monoclonal anti-EGFR antibodies cetuximab and panitumumab. Specific mutations in the ECD of *EGFR* result in reduced mAb binding to the receptor and loss of response to these agents in clinical studies (25, 26). The first *EGFR*-ECD mutation noted that resulted in decreased binding was identified in patients who developed resistance to cetuximab but retained binding to panitumumab (44). Since this observation, several additional mutations resulting in decreased binding of either or both cetuximab and panitumumab have been identified and have been shown to be associated with acquired resistance in patients with mCRC who had received these therapies (26, 45-47).

Other Factors

A variety of other factors have been identified that are associated with innate and/or required resistance to therapy with anti-EGFR mAbs in patients with mCRC (48, 38-42). These include but are not limited to: (a) mutations in other elements of downstream EGFR signal transduction (e.g., *ERBB2, PIK3CA, MEK1, FGFR1, PDGFRA*); (b) gene amplification of *MET* and *ERBB2*; and (c) lower expression of EGFR ligands, including amphiregulin (AREG) and epiregulin (EREG) (25, 26, 41, 42).

2.1.3 Target Patient Population

2.1.3.1 Current Recommendation for Treatment of mCRC with anti-EGFR mAbs

Approved mAbs directed against the EGFR, cetuximab and panitumumab, provide significant survival benefit to patients with WT *KRAS* (exon 2, 3, and 4) and *NRAS* (exon 2, 3, and 4) mCRC, and are now standard components of treatment regimens for these patients, either alone

or in combination with chemotherapy (2-8). Unfortunately, the clinical efficacy of anti-EGFR mAbs is limited by innate as well as the emergence of acquired resistance that eventually develops in all initially responding tumors due to a variety of mechanisms.

2.1.3.2 Prior Results with Sym004: Genomic Selection of a Responsive Patient Subset

Phase 1 results (Sym004-01) documented that Sym004 was well tolerated at doses up to 12 mg/kg weekly, and provided initial evidence of anti-tumor activity in expansion cohorts exploring different doses and schedules in patients with mCRC previously treated with anti-EGFR mAbs (49). The adverse event (AE) profile was similar to the approved anti-EGFR antibodies, although increased frequency and severity of two mechanism-based toxicities (dermatologic toxicity and hypomagnesemia) were observed at the highest doses evaluated.

A recently completed Phase 2b randomized, controlled study (Sym004-05) compared two dose levels of Sym004 (12 mg/kg weekly and a 9 mg/kg loading dose followed by weekly doses of 6 mg/kg) (9/6 mg/kg) versus Investigator's Choice (IC) of 5-FU, capecitabine, or best supportive care (BSC) (50). Patients entered in this trial had to: have prior documentation that their tumors were *KRAS* WT (exon 2); be refractory to or intolerant of standard chemotherapy regimens including fluoropyrimidines, irinotecan and oxaliplatin; and have initially responded to (with a complete response [CR], partial response [PR], or stable disease [SD] > 16 weeks) and progressed on therapy with an anti-EGFR mAb within 6 months of protocol entry. Prior therapy with anti-angiogenic agents was allowed, but patients who had received prior therapy with regorafenib were excluded.

Blood samples were obtained at baseline for analysis of biomarkers in ctDNA (by *Guardant360*® analysis, Guardant Health). The parameters evaluated were based on preclinical models and published clinical data on changes known to impact the response to anti-EGFR mAbs in mCRC patients. These assessments were utilized to evaluate the effects of known genomic parameters on potential clinical benefit from Sym004 treatment. Although the trial did not meet its primary endpoint of improved overall survival (OS) for the Sym-004 Arm versus IC, genomic analyses defined a highly responsive subset of mCRC patients appropriate for further study in subsequent trials. This population excludes patients with high levels of mutations associated with resistance, or acquisition of mutations that are also predicted to impact Sym004 binding. This subpopulation is identified by:

- absence of mutation allele frequency (MAF) of $\geq$ 20% for *KRAS* (exon 2, 3 and 4) and *NRAS* (exon 2, 3 and 4);
- absence of a specific mutation of the *BRAF* gene at amino acid position 600 (*BRAF* V600E); and
- absence of specific *EGFR*-ECD mutations (*EGFR* V441D, V441G, S464L, G465E, G465R, or S492R)

Evaluation of patients with available genomic data who were without the specified mutations (a group termed as having triple-negative mCRC [TNmCRC]) showed an improved median survival when treated with 12 mg/kg (10.6 months) and 9/6 mg/kg (12.8 months) of Sym004, compared to patients in the IC Arm (7.3 months) (50). The results of these exploratory analyses support further evaluation of the Sym004 9/6 mg/kg dosing regimen (Sym004-12) as well as an evaluation of the individual antibodies constituting Sym004 (Sym004-13).

In Sym004-13, a randomized trial in third-fourth line therapy of TNmCRC, Sym004 will be compared to either futuximab or modotuximab, the antibodies that are combined to constitute Sym004. The study is designed to provide evidence of the individual contributions of futuximab and modotuximab to the antitumor activity observed with Sym004.

2.2 Overview of the Product: Sym004

2.2.1 Description of Sym004

The Investigational Medicinal Products (IMPs) tested in this trial are Sym004, futuximab, and modotuximab, the individual antibodies constituting Sym004.

Sym004 is a 1:1 mixture of the two recombinant, human-mouse chimeric, immunoglobulin G1 (IgG1) antibodies (futuximab and modotuximab), which bind specifically to non-overlapping epitopes located in the ECD of EGFR. Each antibody is manufactured individually as a drug substance, and the Sym004 drug product is prepared as a 1:1 ratio mixture of the two. Sym004, futuximab, and modotuximab are each clear to opalescent, colorless to slightly yellow, solutions to be administered via intravenous (IV) infusion through an indwelling catheter.

2.2.2 Mechanism of Action of Sym004 and the Individual Antibodies

The simultaneous binding to EGFR of both antibodies contained in Sym004 induces a distinct mechanism of action. Sym004 induces highly efficient internalization of EGFR on cancer cells, followed by degradation of the internalized receptor-antibody complexes that leads to down-regulation of EGFR and subsequent inhibition of cancer cell growth (51). There is considerable preclinical *in vitro* and *in vivo* evidence suggesting that Sym004 is superior to the marketed anti-EGFR antibodies, cetuximab and panitumumab, in a wide range of cancer models (51, 52). Sym004 has also demonstrated activity in cancer cells with acquired resistance to cetuximab (53, 54). As described, in the completed Phase 2b study of two dose levels of Sym004 versus IC, there was evidence of survival prolongation in a genomically-defined population who had previously responded to and then progressed during or within 6 months of completion of prior anti-EGFR mAb therapy (50).

The binding region of futuximab on the EGFR is similar to that of cetuximab and panitumumab and the mode of action of futuximab includes inhibition of cancer cell growth and survival by blocking ligand-binding, receptor activation and phosphorylation, and downstream receptor signaling. In contrast, futuximab binds a conformational epitope that is less accessible on the EGFR compared to the epitopes of cetuximab and panitumumab, and hence requires higher concentrations for maximum activity. Modotuximab only weakly blocks ligand binding and has limited effects on receptor activation and tumor cell growth. The primary mode of action of modotuximab is to stabilize a conformation of EGFR to which futuximab binds with much higher affinity than to the native conformation, thus inducing the simultaneous strong binding of both antibodies in Sym004 to EGFR.

2.3 Summary of Nonclinical Studies

A series of *in vitro* and *in vivo* studies were performed to support clinical trials (51-54). The ability of futuximab, modotuximab, and Sym004 to inhibit proliferation and motility of cancer cells was investigated *in vitro* and *in vivo* in a range of human cancer cell lines and patient-derived xenografts, and compared to cetuximab and/or panitumumab (51-53). The effect of

Sym004 on cells with acquired resistance to cetuximab was also investigated (53), including studies of *EGFR*-ECD mutated cell lines and xenograft models. Mechanistic studies of Sym004 action performed in a panel of human cancer cell lines included assessment of inhibition of ligand binding, EGFR activation, and downstream signaling, as well as effects on EGFR internalization and degradation (51). Futuximab-, modotuximab-, and Sym004-mediated secondary effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were investigated in human cancer cell lines (52).

Collectively, all these studies showed that while futuximab and modotuximab demonstrate some tumor growth inhibitory activity as single agents, Sym004 was clearly superior at inhibiting EGFR activity and tumor growth. Likewise, Sym004 was as good or better than the reference monoclonal antibodies, cetuximab and panitumumab, at inhibiting tumor growth *in vitro* and *in vivo* (51, 52).

Toxicology studies in cynomolgus monkeys showed a profile for Sym004 consistent with other anti-EGFR antibodies, including documentation of dermatologic and gastrointestinal toxicities (55). Administering futuximab and modotuximab as separate antibodies at 7 mg/kg resulted in less toxicity than administering 7 mg/kg Sym004 (3.5 mg/kg of each antibody).

Nonclinical pharmacokinetic (PK) studies indicate that the efficient down-modulation of EGFR observed after administration of futuximab and modotuximab in combination as Sym004 has an impact on the PK parameters (55). A dose of 7 mg/kg of Sym004 administered to cynomolgus monkeys was cleared rapidly with a serum elimination half-life ($T_{½}$) of 1-3 days, and on repeated weekly dosing no accumulation was observed. In contrast, the $T_{½}$ after administration of 7 mg/kg of either futuximab or modotuximab was longer and evidence of drug accumulation was noted on repeated weekly dosing. These findings suggest that the Sym004 antibody combination results in more rapid elimination due to enhanced target-mediated drug disposition. Conversely for futuximab and modotuximab, the target-mediated drug disposition was less pronounced, which could be explained by a less potent binding and internalization of EGFR when the antibodies are dosed separately. As a consequence, the individual antibodies, when administered as single agents, may accumulate resulting in higher serum levels compared to a similar dose of the individual antibodies administered as Sym004.

2.4 Clinical Experience

Several clinical trials have been completed with Sym004, and others are being planned. This is the first clinical study in which the individual antibodies, futuximab and modotuximab, are being administered to patients as single agents. These two antibodies have been administered as a combination in all human studies of Sym004 thus far. In this study, the individual antibodies will each be administered at the same dose (4.5 mg/kg loading dose followed by 3 mg/kg weekly) as contained in the planned dose of Sym004 (9 mg/kg loading dose followed by 6 mg/kg). Since weekly dosing of up to 12 mg/kg of Sym004 has been studied without evidence of dose limiting toxicities in over 100 patients, dose escalation of the individual antibodies is not warranted.

2.4.1 Safety

As of January 2018, approximately 380 patients with solid tumors have been exposed to Sym004 in completed and ongoing Symphogen-sponsored trials, and 30 patients have been exposed to Sym004 in an investigator-initiated trial in patients with recurrent glioblastoma (Sym004-08). In

Phase 1 and Phase 2 studies in a variety of indications, patients have been exposed to weekly doses of up to 12 mg/kg, and in every second week doses of up to 18 mg/kg.

The most common adverse reactions (i.e., AEs considered treatment-related by the investigator) in completed Symphogen-sponsored studies with a frequency of ≥ 10% are shown below, along with the percentage of those reactions that were ≥ Grade 3 in severity shown in parentheses (**Table 1**):

Table 1: Sym004 Adverse Events ≥ 10%

percentage of reactions ≥ Grade 3 shown in parentheses	
Skin-related reactions of:	
acneiform rash	57.6% (24.1%)
pruritus	34.3% (1.6%)
rash	31.6% (14.1%)
dry skin	26.2% (2.4%)
paronychia	20.5% (1.1%)
skin fissures	20.0% (3.0%)
xerosis	16.8% (1.9%)
erythema	15.4% (3.5%)
Infusion-related reactions	17.8% (1.6%)
Electrolyte imbalances including:	
hypomagnesemia*	65.7% (23.8%)
hypocalcemia	13.2% (2.4%)
hypokalemia	10.0% (1.9%)
Gastrointestinal symptoms including:	
diarrhea	25.4% (2.2%)
decreased appetite	20.8% (1.1%)
nausea	17.8% (0.5%)
stomatitis	12.7% (0.8%)
mucosal inflammation	12.7% (0%)
constipation	11.6% (0.3%)
abdominal pain	11.4% (2.2%)
vomiting	10.8% (0.8%)
Asthenia	27.0% (5.7%)
Fatigue	13.5% (3.5%)
Pyrexia	12.4% (0.5%)
Anemia	16.5% (4.6%)
Edema peripheral	13.0% (0.8%)

*Includes blood magnesium decreased

In the Sym004-05 study, the AE profile was consistent with other anti-EGFR mAbs, although the frequency and severity of both dermatologic AEs and hypomagnesemia were higher. This trial only included patients who had benefited from prior therapy with cetuximab or panitumumab and they hence also had a higher incidence of dermatologic toxicity, consistent with prior published observations (50). The frequency of gastrointestinal AEs appeared to be lower than has been reported for cetuximab or panitumumab. The frequency of many AEs was higher in patients receiving the 9/6 regimen compared to patients on the IC Arm. Such AEs include:

- Related treatment-emergent AEs (TEAEs) (95.2 vs. 59%)
- Serious TEAEs (27.4 vs. 15.4%)
- Serious-related TEAEs (7.1 vs. 2.6%)
- ≥ Grade 3 TEAEs (63.1 vs. 32.1%)
- Related TEAEs ≥ Grade 3 (48.8 vs. 11.5%)
- TEAEs leading to dose reduction (20.2 vs. 10.3%)

In contrast, the frequency of TEAEs leading to study treatment discontinuation (6.0 vs. 7.7%) and related TEAEs leading to study treatment discontinuation (2.4 vs. 3.8%) was not different in patients treated with Sym004 9/6 and IC, respectively.

These adverse reactions were anticipated and appear to be consistent with the safety profile of other EGFR antagonists such as cetuximab (55) and panitumumab (57). Ongoing monitoring of patients and mitigation strategies to minimize the risk of and to treat these adverse reactions are in place to safeguard patients participating in ongoing and planned studies.

In conclusion, based on the significant unmet need in patients with progressive disease (PD) refractory to other treatment regimens, and the current safety profile, the overall benefit/risk profile of Sym004 appears to be favorable.

Additional data on the safety and tolerability of Sym004, including data on serious adverse events (SAE), are provided in detail in the IB.

2.4.2 Pharmacokinetics

PK analyses have been performed on patients participating in the Phase 1 trial Sym004 in patients with solid tumors (Sym004-01), in the Phase 2 trial in patients with squamous cell carcinoma of the head and neck (Sym004-02), and in the Phase 2b trial in patients with mCRC (Sym004-05) (50). In the Phase 1 trial, serum levels of Sym004 increased in a dose-dependent manner during the dose-escalation phase which evaluated weekly Sym004 dose levels ranging from 0.4 to 12 mg/kg. Doses of < 3 mg/kg were rapidly cleared from the circulation. A dose-dependent, nonlinear increase in $T_{½}$ was observed. The geometric mean $T_{½}$ was approximately 3 days after doses of 12 mg/kg and 5 days after doses of 18 mg/kg. The two antibodies constituting Sym004 displayed similar serum elimination profiles (55).

Data from the trials also documented that the two antibodies constituting Sym004 were generally present in serum in close to a 1:1 ratio at each visit. The calculated $T_{½}$ increased from the first to the fourth infusion of Sym004, with comparable increases in maximum concentration (C_{max}) and the calculated area under the concentration-time curve (AUC). The observed increase in exposure was considered to be consistent with saturation of the elimination mechanism proceeding via the antibody target (the EGFR) after repeated dosing of Sym004.

In Sym004-05, the serum concentration of Sym004 at predose (trough) and end of infusion (EOI) (peak) were assessed Week 3, 5 and 7 and at the end of treatment visit (EOT). The trough serum concentration of Sym004 for the 9/6 mg/kg did not change with time between Week 3 and Week 7, indicating that steady state was obtained after the first few dose administrations. For 12 mg/kg as well as 9/6 mg/kg, the trough and peak values in Weeks 5 and 7 were generally comparable to those of comparable dose regimens in Sym004-01.

More complete PK analyses data are included in the Investigator's Brochure (IB).

2.4.3 Pharmacodynamic Effects

Tumor and skin biopsies were obtained before the first and planned fifth infusions of Sym004 in the Sym004-01 trial in patients with mCRC resistant to anti-EGFR antibody therapy. Decreases in membranous EGFR levels and in the proliferation marker, Ki67, were observed in both tumor and skin biopsies (49). These data provided clinical proof that Sym004 at the doses administered distributed to tumor, inhibited the intended target, and suppressed a known marker of tumor cell proliferation.

2.4.4 Antitumor Effects

As a part of the Phase 1 dose-escalation trial (Sym004-01), antitumor activity was documented in patients with mCRC resistant to anti-EGFR antibody therapy (49). Five of the 39 documented refractory patients (13%) with adequate imaging studies achieved a PR. These responses were confirmed by independent radiologic review. A PR or disease stabilization was documented in 67% of patients with available assessments.

From the Phase 2b trial (Sym004-05), an exploratory analysis revealed that the responders to Sym004 had tumors with WT *KRAS*, *NRAS*, and *BRAF* genotype, as well as having no evidence of *MET* amplification. The antitumor results of this trial are described in **Section 2.1.3.2**.

2.5 Trial Rationale

Patients with mCRC resistant to standard combination regimens including fluoropyrimidines, irinotecan, oxaliplatin, anti-angiogenic agents, and anti-EGFR mAbs have relatively few therapeutic options. Survival decreases with each line of therapy in patients with this life-threatening malignancy. Currently, in the third- and fourth-line therapy settings the best OS results are in the range of 7-8 months. A subset of patients with MSI-H/dMMR mCRC may benefit from therapy with an antibody to programmed cell death protein-1(PD-1) (13, 14). The incremental benefit and OS observed with the two newer orally administered agents, regorafenib and TAS-102 compared to placebo and BSC in large Phase 3 studies (9) were 1.4 and 6.4 months and 1.8 months and 7.4 months, respectively (11). Given the limited options and relatively minor improvements in OS in the trials of these recently approved agents in treatment-refractory mCRC patients, additional therapeutic options are of great interest.

There is considerable preclinical *in vitro* and *in vivo* evidence that suggests Sym004 to be superior to existing anti-EGFR antibodies (cetuximab and panitumumab) in a wide range of cancer types (51-54). Preliminary evidence of the antitumor activity of Sym004 in patients with mCRC refractory to standard chemotherapy, and who had received previous therapy with anti-EGFR mAbs, has been documented in Phase 2 expansion cohorts evaluating a variety of doses and schedules (49). Although the overall trial (Sym004-05) did not meet the primary efficacy endpoint of a 3-month improvement in OS with either Sym004 Arm (12 and 9/6 mg/kg) when compared to the IC Arm, subsequent hypothesis-generating sub-analyses supporting the secondary objective of identifying biomarkers predictive of clinical benefit in patients treated with Sym004 yielded a discrete genetic signature that confers significant benefit in terms of OS. Positive signals of clinical benefit in patients with treatment-resistant/refractory TNmCRC (no *RAS* MAF $\geq$ 20%, no *BRAF* V600E and no *EGFR*-ECD mutations) were observed in the Sym004-05 study. The subpopulation analysis showed that patients with TNmCRC had an OS

benefit of 5.5 months when compared to the IC Arm, with a hazard ratio of 0.59. These results will require confirmation in a planned Phase 3 randomized controlled trial.

Although preclinical data have clearly documented superiority of Sym004 compared to anti-EGFR reference antibodies, cetuximab and panitumumab, and the two antibodies, futuximab and modotuximab in the Sym004 mixture, there is no direct clinical evidence that these preclinical data will translate into clinical superiority in patients with advanced, treatment-refractory mCRC. The predictive value of preclinical *in vitro* and *in vivo* studies in determining clinical efficacy is relatively limited (58-60). One of the many reasons for the failure of preclinical models to accurately predict clinical efficacy in patients is the heterogeneity of individual malignancies, including mCRC (26), as well as their evolution over time (61-66). For this reason, this Phase 2, randomized, controlled trial is being undertaken to evaluate the safety, PK profiles, and preliminary antitumor activity (as measured by tumor shrinkage) of Sym004 and its individual component mAbs, futuximab and modotuximab.

2.6 Dose Rationale

Based on the results from the Sym004-01 and Sym004-05 trials, a Sym004 dosing regimen of 9 mg/kg loading, followed by 6 mg/kg/week has been chosen for this trial. This dosing regimen was administered to 20 patients in Sym004-01 and to 84 patients in Sym004-05 and resulted in a tolerable safety profile, with dermatologic toxicities and hypomagnesemia as the most frequent ≥ Grade 3 AEs. In Sym004-01 the median duration of treatment for patients on this regimen was 9.0 weeks (min 2.1 and max 50.9). Median progression-free survival (PFS) was 2.3 months, median time to progression was 3.1 months, and median OS was 9.6 months. In Sym004-05, the median duration of treatment for patients receiving the 9/6 regimen was 11.9 weeks (min 1 and max 77). Median PFS was 2.7 months and median OS was 10.3 months in the intent-to-treat (ITT) population from this larger Phase 2b randomized, active controlled trial.

Futuximab and modotuximab dosing regimens of 4.5 mg/kg loading, followed by 3 mg/kg/week have been chosen for this trial to reflect the dose levels of the individual antibodies in the Sym004 mixture. The safety profile of futuximab and modotuximab is expected to be tolerable based on data obtained with Sym004.

2.7 Summary of Overall Benefit and Risk

As previously discussed, preclinical data in addition to preliminary clinical data in patients 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 approximately 30% of patients at doses of 9 mg/kg/week (n=13) and 12 mg/kg/week (n=29) were observed. Preclinical data have also shown some activity of the individual antibodies and although they appear to be less potent as single agents than the mixture in Sym004, this may not be predictive for clinical activity. One or both antibodies administered alone may demonstrate a clinical activity similar to that of Sym004.

In previous clinical trials, Sym004 demonstrated an acceptable safety profile. The safety profile is similar to that of other anti-EGFR antibodies, although the percentage of patients with Grade 3 dermatologic AEs and Grade 3 or Grade 4 hypomagnesemia appeared to be higher.

Based on the results from the Sym004-01 and Sym004-05 trials, a Sym004 dosing regimen of 9 mg/kg loading dose, followed by 6 mg/kg/week was found to be acceptable and data from both of these trials provided preliminary evidence of activity (**Section 2.6**).

Prophylactic and reactive treatment guidelines for dermatologic management are included in this current study to reduce the incidence of severe rash (**Appendix 7**). Based on data derived from a randomized controlled trial using this approach, e.g., skin toxicity evaluation protocol with panitumumab (STEPP) trial (67), 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 refractory to standard therapies, including anti-EGFR antibodies, and what is currently known about the safety profile for Sym004, the benefit-risk relationship has been carefully considered in the planning of this trial. Based on the preclinical and clinical data available to date, the conduct of the trial is considered justifiable when using the dose and dosage regimens of Sym004, futuximab, and modotuximab as specified in this clinical trial protocol. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the benefit-risk relationship that would render continuation of the trial unjustifiable.

FOR ADDITIONAL INFORMATION, PLEASE REFER TO THE IB

3 TRIAL OBJECTIVES AND DESIGN

3.1 Objectives

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as detailed below are no longer applicable. Only clinical safety-related evaluations will be conducted.

3.1.1 Primary Objective

To evaluate the relative contribution of futuximab and modotuximab to the antitumor activity* of Sym004 following 8 weeks of treatment in genomically-selected** patients with chemotherapy refractory metastatic colorectal carcinoma (mCRC) and acquired resistance to anti-EGFR mAb therapy.

*As assessed by changes in tumor measurements; evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (**Appendix 5**).

**Genomic analysis by *Guardant360* to be performed at prescreening for assessment of *RAS (KRAS/NRAS)*, *BRAF* V600E, and *EGFR*-ECD mutation status.

3.1.2 Secondary Objective

To evaluate the safety profile of a weekly dosing regimen of Sym004 versus single agent futuximab or single agent modotuximab

3.1.3 Exploratory Objective

To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood, skin biopsies, and tumor biopsies to be collected). Tumor biopsies will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models.*

3.2 Trial Design Summary

As of Amendment 5: This amendment to the clinical trial protocol is based on the Sponsor's decision to discontinue the trial for administrative reasons, effective 20Dec2018; the intent to discontinue the trial was communicated to all active sites on this date. As a result, the original trial design as described below is no longer applicable, future accrual has been halted, and a reduction in the scope of non-safety-related assessments being conducted under this protocol has been implemented.

Patients consented as of the trial discontinuation date, and determined to meet study eligibility criteria, may be treated with IMP and may continue therapy until the occurrence of one of the following: unacceptable toxicity or other conditions preventing further administration, documented PD, or the patient's decision to withdraw.

- Treated patients will be followed and assessed for only clinical safety-related concerns.
- Of the Specialty Assessments initially planned: ADA and samples for exploratory PK and PD assessments (in peripheral blood, skin biopsies, and tumor biopsies) will not be collected; genomic samples for eligibility assessment were obtained at prescreening and analyzed, however post-dosing genomic samples will not be collected.
- The frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion until confirmation of PD.

The visit schedule for safety assessments will apply as specified elsewhere in this clinical trial protocol. Once IMP has been discontinued, an EOT visit will be performed within 7 to 10 days from the decision to withdraw treatment, and a 1M FUP visit will be performed 30 days (+7 days) following the last dose.

The pre-Amendment 5 trial design was as follows:

Patient Population

This is a Phase 2, open-label, three-Arm trial with randomization in the ratio of 1:1:1 to either Sym004 (Arm A), futuximab drug product (Arm B), or modotuximab drug product (Arm C) in genomically-selected patients with chemotherapy refractory mCRC and acquired resistance to anti-EGFR mAb therapy. The study is designed to evaluate the relative antitumor activity of each agent following 8 weeks of treatment, as assessed by imaging studies and tumor measurements performed at the end of Cycle 2 (EOC2). Following the EOC2 assessment, ongoing patients from Arm A will continue to receive Sym004; ongoing patients from Arm B and Arm C will be crossed-over from futuximab or modotuximab to receive Sym0004.

Approximately 54 evaluable male and female patients, 18 per Arm, with mCRC and measurable disease according to RECIST criteria will participate in this trial. Following consent and prior to randomization, centralized genomic analysis of *RAS (KRAS/NRAS)*, *BRAF* V600, and *EGFR*-ECD mutations in ctDNA from peripheral blood samples obtained from each potential patient will be conducted. Triple-negative (TN) mutation status as defined in trial eligibility criteria will be required for initial eligibility.

Patients with TNmCRC will continue in the screening process. Site Investigators will evaluate patients for eligibility and submit relevant information. Designated Eligibility Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization. Once authorization is obtained, patients will be randomized to Arm A, Arm B, or Arm C.

Dosing Schedule

Cycle 1 dosing will occur ≤ 3 days (72 hours) after randomization. Beginning with the first dose, all patients will be premedicated with standard therapies prior to each dose to reduce the risk of infusion-related reactions (IRRs), and must be premedicated with standard therapies throughout at minimum Cycles 1 and 2 to reduce the risk of anti-EGFR-related dermatologic adverse events (AEs).

Dosing will be as follows:

- Patients randomized to Arm A will receive Sym004 by the intravenous (IV) route, at a loading dose of 9 mg/kg on Cycle 1 Day 1 (C1D1) followed by weekly doses of 6 mg/kg beginning on C1D8 (total of 4 doses per 28-day cycle).

- Patients randomized to Arm B or Arm C will receive futuximab or modotuximab, respectively, by the IV route, at a loading dose of 4.5 mg/kg on C1D1 followed by weekly doses of 3 mg/kg beginning on C1D8 (total of 4 doses per 28-day cycle).

Patients in both Arms will be treated and followed on an outpatient basis throughout the trial, unless hospitalization is required for other reasons, or to ensure patient safety.

Treatment Duration

Patients will continue dosing cycles of 28 (± 2) days, provided specified retreatment criteria are met, until documented disease progression or the occurrence of unacceptable toxicity or another criterion necessitating discontinuation from the treatment. Antitumor activity will be assessed at the end of every 2 cycles (every 8 weeks [Q8W]).

At the EOC2 tumor assessment:

- Patients assigned to Arm A (Sym004) with a documented objective response (OR) or SD will continue to receive Sym004; patients with documented PD at the EOC2 will be discontinued from the study;
- Patients assigned to Arm B (futuximab) or Arm C (modotuximab) with a documented OR or SD will be crossed-over to receive Sym004; patients with documented PD at the EOC2 (or prior to the EOC2) will be offered the opportunity to crossover to receive Sym004 or will be discontinued from the study. Dosing of Sym004 may continue until further PD is observed.

Criteria for Evaluability

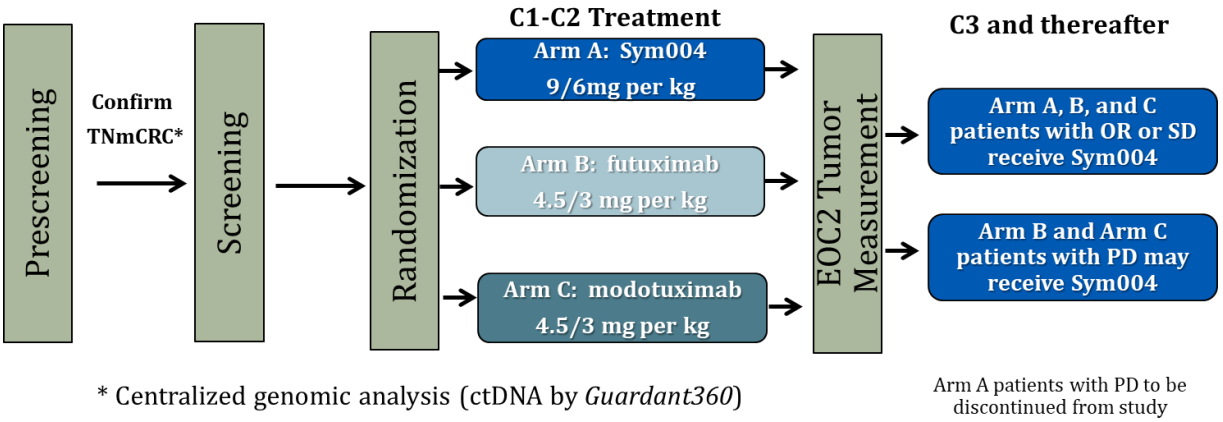
To be considered evaluable for antitumor activity assessment, patients must have completed 2 cycles of dosing inclusive of EOC2 disease imaging studies (i.e., computed tomography [CT]/magnetic resonance imaging [MRI]), and must have received any amount of their assigned investigational medicinal product (IMP) during that period, or have PD documented by imaging studies prior to the EOC2. Nonevaluable patients and patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD will not be replaced *(every effort will be made to obtain imaging studies at the time of discontinuation)*.

Safety Monitoring

Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigator(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held at intervals to discuss ongoing patient status and any emerging safety concerns.

The overall trial schema is shown in **Figure 1**.

Figure 1: Trial Design



Abbreviations (in alphabetical order): 9/6 mg per kg, 9 mg loading dose followed by weekly doses of 6 mg/kg ; C, cycle; ctDNA, circulating tumor DNA; EOC2, end of cycle 2; kg, kilogram; mg, milligram; OR, objective response; PD, progressive disease; SD, stable disease; TNmCRC, triple negative metastatic colorectal carcinoma

Study Assessments

For safety, patients will be monitored throughout the treatment and 1-month follow-up (1M FUP) period for changes in: clinical status, physical examination findings (including weekly assessments for dermatologic AEs); laboratory data (including weekly assessments for hypomagnesemia, hypocalcemia, and hypokalemia); and electrocardiogram (ECG) findings. Patients will be evaluated for evidence of acute as well as cumulative or delayed toxicities. Patients will also be evaluated for evidence of the development of antidrug antibodies (ADA) to IMP, and PK sampling will be performed to enable population PK modeling and to evaluate potential PK differences between Sym004, futuximab, and modotuximab as observed in nonclinical studies.

For evaluation of the antitumor effects of Sym004, futuximab, and modotuximab, patients will undergo imaging studies and disease response assessments approximately every 8 weeks (Q8W), at the end of even-numbered cycles. Confirmed PD, as defined by RECIST v1.1, following initial treatment (Arm A) or after crossover treatment with Sym004 for patients in Arm B or Arm C will necessitate withdrawal of the patient from study so that alternative management of their malignancy may be considered. Antitumor effects observed in patients on all three Arms at the end of Week 8 (EOC2) will be assessed to evaluate potential differences between Sym004 and futuximab and modotuximab. Subsequent imaging studies will be performed as a part of standard practice for patient management.

Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing, including at the time of documented progression or study discontinuation for other reasons, in skin biopsies obtained prior to first dose and following Cycle 1 and Cycle 2 dosing, and in tumor biopsies obtained prior to first dose and following Cycle 2 dosing.

The overall trial plan is introduced in **Table 2**.

Table 2: Overall Trial Plan	
Prescreening	**Must have progressed from prior therapy**
Genomic Analysis (prescreening)	• Written informed consent *(within 28 days prior to 1st dose; may be extended to allow for receipt of genomic analysis results, or collection of sample for genomic analysis may be performed under a separate ICF)* • Centralized ctDNA analysis by *Guardant360*
Screening	**Patients with confirmed TNmCRC only**
Disease Status and Safety Evaluation (screening)	• Disease status evaluation *(imaging studies may be used to document tumor status at screening if performed within 14 days prior to 1st dose)* • Safety evaluation (*within 14 days prior to 1st dose unless otherwise stipulated*)
Randomization	**Patients confirmed/authorized as fully eligible**
Treatment Assignment	• Randomization to Sym004 versus futuximab versus modotuximab *(within 14-day screening window; C1D1 dosing to occur ≤ 3 days (72 hours) after randomization)*
Treatment Period	
Treatment	• C1D1 initial dose of IMP • 28-day cycles until confirmed PD, unacceptable toxicity, or another discontinuation criterion is met • Tumor assessment at EOC2 with continuation of Sym004, or crossover to Sym004, as indicated • EOT visit within approximately 7 to 10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first • 1M FUP visit 30 days (+7 days) following last dose* **Completion of the 1M FUP visit will be considered the end of study for the patient unless additional safety follow-up is required*
Follow-up Period	
Post-Treatment Follow-up	• Safety FUP if an IMP-related AE has not resolved by the 1M FUP *(2 months [4 months if necessary] following last administration of IMP)*

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; C1D1, Cycle 1 Day1; ctDNA, circulating tumor DNA; EOT, end of treatment; FUP, follow-up; ICF, informed consent form; PD, progressive disease; Q2M, every 2 months; Q2W, every 2 weeks

4 PATIENT SELECTION

4.1 Number of Patients

As of Amendment 5: As of the trial discontinuation date (20Dec2018), a single center in the United States had consented and screened patients. Two (2) of 5 patients screened were determined to be eligible for participation and both were enrolled in the study. The total number of sites planned will not be participating; the total number of patients planned will not be enrolled.

4.1.1 Investigational Sites

This is a multicenter, multinational trial.

- Number of Sites: Approximately 20 sites may participate based on anticipated accrual
- Number of Countries: Approximately 4-6 countries in North America and Europe

4.1.2 Planned Sample Size

Up to approximately 54 evaluable patients (18 evaluable patients per Arm)

Note: To be considered evaluable for antitumor activity assessment, patients must have completed 2 cycles of dosing inclusive of EOC2 disease imaging studies and must have received at least 6 of 8 doses of their assigned IMP during that period or have PD documented by imaging studies prior to the EOC2. Non-evaluable patients and patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD, will not be replaced.

4.2 Criteria for Inclusion

As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; however, patients consented prior to the effective date will be required to meet the following inclusion criteria:

(Patients must meet all of the following criteria)

1. Male or female patients, ≥ 18 years of age at the time of obtaining informed consent
2. Patients with histologically- or cytologically-confirmed mCRC
3. Patients with MSI-H/dMMR tumors must have received prior therapy with pembrolizumab, nivolumab, or other PD-1/PD-L1 pathway blocker, and must have progressed on that therapy.
4. Patients meeting the protocol definition of TNmCRC assessed by screening blood test (ctDNA):
    a. Without *RAS* (*KRAS* and *NRAS*) MAF ≥ 20% for mutations in the following codons:
        - Exon 2: codon 12, 13
        - Exon 3: codon 59, 61
        - Exon 4: codon 117, 146
    b. Without *BRAF* V600E mutation at any MAF

c. Without *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations at any MAF

Note: Centralized genomic analysis to be performed; peripheral blood to be collected for assessment of ctDNA by Guardant360.

5. Patients with mCRC currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor
6. Patients with measurable disease according to RECIST v1.1 (**Appendix 5**), and willingness to undergo a total of 2 biopsies of a primary or metastatic tumor site(s) considered safely accessible for biopsy
7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed (includes intolerance to) those regimens

   Prior standard chemotherapy may not have included TAS-102 or regorafenib, but must have included all of the following agents (where approved in the country):

   a. Fluoropyrimidines, irinotecan, and oxaliplatin
   b. An anti-vascular endothelial growth factor (VEGF) pathway inhibitor approved for treatment of mCRC
   c. At least one anti-EGFR mAb approved for treatment of mCRC

   Note: Patients who withdrew from standard therapy(ies) due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will be eligible to enter the study.

   Patients who received adjuvant chemotherapy and had documented recurrence (by imaging studies) during or within 6 calendar months of completion of the adjuvant chemotherapy are permitted to count the adjuvant therapy as one regimen of chemotherapy.

8. Patients with “acquired” resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC. Patients must have:

   a. Received treatment with an anti-EGFR for >16 weeks
   b. PD documented by imaging or clinical findings $\leq$ 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 treatment to date of consent for this trial (regardless of the line of therapy in which it was used)

9. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (or equivalent Karnofsky PS; **Appendix 1**)
10. Patients, male and female, who are either not of childbearing potential or who agree to use a highly effective method of contraception during the study beginning within 2 weeks prior to the first dose and continuing until 3 months after the last dose of IMP.

    Note: Women are considered of childbearing potential unless they have undergone hysterectomy and/or bilateral tubal ligation or oophorectomy, or have been postmenopausal for at least one year. Postmenopausal status in females under 55 years who have not been surgically sterilized should be

confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.

A highly effective method of contraception is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide) or intrauterine device (**Section 11.1**).

Women of childbearing potential (WOCBP) must have a negative pregnancy test within ≤ 2 working days prior to administration of the first dose of IMP.

11. Must have the ability to understand and give written informed consent for participation in this trial, including all evaluations and procedures as specified by this protocol

    Note: Informed consent must be obtained prior to patient screening, and before any evaluations or procedures specifically related to this study are performed.

4.3 Criteria for Exclusion

As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; however, patients consented prior to the effective date will be required to meet the following exclusion criteria:

4.3.1 Patients to be Excluded

(Patients must not meet any of the following criteria)

1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 3 months after the last dose of IMP. WOCBP, and fertile men with WOCBP-partner(s) not using and not willing to use a highly effective method of contraception.

   Note: WOCBP includes any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is not postmenopausal. Post-menopause is defined as: 1) amenorrhea for > 12 months with no other cause, or 2) irregular menstrual periods, on hormone replacement therapy (HRT), with a documented FSH level > 35 mIU/mL.

   WOCBP and fertile men will be informed as to the potential risk of procreation while participating in this trial. A pregnancy test will be performed, and the results reviewed, on each premenopausal WOCBP prior to first IMP administration. A negative pregnancy test performed within **≤ 2 working days** prior to first IMP administration must be documented on the patient's case report form (CRF) (**Section 11.1**).

2. Patients with a prior history any of the following mutations in their tumor at the time of any previous assessment:
   a. *RAS* (*KRAS* and *NRAS*) mutations in the following codons:
      - Exon 2: codon 12, 13
      - Exon 3: codon 59, 61
      - Exon 4: codon 117, 146

   b. *BRAF* V600E mutation

   c. *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations

3. Patients with known, untreated central nervous system (CNS) or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior

surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required

Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids or anticonvulsants, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed ≥ 4 weeks apart with the most recent performed within 4 weeks prior to first IMP administration.

Patients with newly identified CNS disease during study treatment will be considered to have PD and will be discontinued from treatment.

4. Patients with an active second malignancy or history of another malignancy within the last 5 years with the exception of:
    a. Treated non-melanoma skin cancers
    b. Treated carcinoma *in situ* (e.g., breast, cervix, endometrium) provided CR was achieved at least 5 years prior to study and no additional therapy is ongoing or required during study period)
    c. Controlled, superficial carcinoma of the bladder
    d. T1a carcinoma of the prostate comprising < 5% of resected tissue and prostate specific antigen (PSA) within normal limits (WNL) since resection
5. Patients with any of the following hematologic abnormalities at baseline*:
    a. Hemoglobin < 9.0 g/dL
    b. Absolute neutrophil count (ANC) < 1,500 per mm^3
    c. Platelet count < 100,000 per mm^3

    Note: Patients may have received a blood/blood product transfusion prior to study, if clinically warranted.

    **Throughout this protocol "baseline" is defined as the last available observation prior to the first administration of IMP on C1D1.*
6. Patients with any of the following serum chemistry abnormalities at baseline:
    a. Total bilirubin > 2.0 × the upper limit of normal (ULN) for the institution
    b. Alkaline phosphatase (ALP) > 2.5 × the ULN for the institution (> 5 × ULN if due to hepatic involvement by tumor)
    c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × the ULN for the institution (> 5 × ULN if due to hepatic involvement by tumor)
    d. Creatinine clearance (Cr_{Cl}) < 30 mL/min as calculated by the Cockroft-Gault formula
    e. Magnesium < 1.2 mg/dL
7. Patients with:

a. Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), within 4 weeks prior to first administration of IMP, unless adequately treated and considered by the Investigator to be stable

b. Active uncontrolled bleeding or a known bleeding diathesis

8. Patients with a known clinically significant cardiovascular disease or condition, including:
    a. Need for antiarrhythmic medical therapy for a ventricular arrhythmia or other uncontrolled arrhythmia (patients with controlled atrial fibrillation (heart rate < 90) for > 30 days prior to study entry are eligible)
    b. Severe conduction disturbance (e.g., 3rd degree heart block)
    c. HR-corrected QT interval (QTc interval) ≥ 480 msec (as calculated by Bazet's formula)
    d. Uncontrolled hypertension (per the Investigator's discretion)
    e. Congestive heart failure currently requiring therapy
    f. Class III or IV cardiovascular disease according to the New York Heart Association Functional Classification (**Appendix 2**)
    g. History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to first administration of IMP
9. Patients with non-healing wounds on any part of the body
10. Patients with a significant gastrointestinal abnormality, including:
    a. Diarrhea > Grade 1* at the time of randomization
    b. Requirement for IV alimentation

    **AE grading based on Common Terminology Criteria for Adverse Events (Version 5) (CTCAE v5)*

    Note: Patients with recent Grade 2 diarrhea secondary to administration of oral contrast are allowed, provided symptoms have resolved prior to first study drug administration.

11. Patients with skin rash > Grade 1 from prior anti-EGFR therapy at the time of randomization
12. Patients with any unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, peripheral neuropathy, and/or end-organ failure being adequately managed by hormone replacement therapy
13. Patients with a known or suspected hypersensitivity to any of the excipients of formulated IMP(s)

14. Patients with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to first study administration of IMP
15. Patients with inadequate recovery from any prior surgical procedure, or patients having undergone any major surgical procedure within 4 weeks prior to first administration of IMP

    Note: Patients having undergone recent placement of a central venous access device or port will be considered eligible for enrollment.

16. Patients with any other serious, life-threatening, or unstable preexisting medical condition (aside from the underlying malignancy), including significant organ system dysfunction, or CS laboratory abnormality(ies), which, in the opinion of the Investigator, would either compromise the patient's safety or interfere with obtaining informed consent, compliance with study procedures, or evaluation of the safety of IMP
17. Patients with a psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary study-related evaluations
18. Patients with the inability or with foreseeable incapacity, in the opinion of the Investigator, to comply with the protocol requirements

4.3.2 Drugs and Other Treatments to be Excluded

(Patients must not be receiving <u>any</u> of the following)

1. Prior treatment with TAS-102 or regorafenib
2. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks prior to first administration of IMP and during study, with the exception of:
    a. Nitrosoureas and mitomycin C within 6 weeks prior to first administration of IMP and during study

    Note: Patients may have received and failed prior therapy with immune modulators (e.g., PD-1, PD-L1 inhibitors) and be considered eligible for this trial.

3. Any other investigational treatments within 4 weeks prior to and during study; includes participation in any medical device or other therapeutic intervention clinical trials
4. Radiotherapy:
    a. For lesions to be used as target lesions, within 4 weeks prior to first administration of IMP unless disease progression has been documented in the lesion post-radiotherapy, and during study
    b. For non-target lesions, within 1 week prior to first administration of IMP

    Note: Palliative (limited-field) radiotherapy for management of pain associated with bone metastases present at baseline is permitted during study. Patients with suspected new bone lesions requiring pain management should be treated and evaluated for potential disease progression.

5. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to first administration of IMP and during study. *The following therapies are allowed*:
    a. Hormonal therapy for appetite stimulation (e.g., Megace)
    b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
    c. Hormone replacement therapy at standard doses for end-organ failure
    d. Stable hormonal therapy for ovarian suppression for non-malignant conditions, hormonal contraceptive therapy, or post-menopausal HRT*
    e. Steroid therapy for contrast reaction prophylaxis
    f. Low-dose maintenance steroid therapy for other conditions (e.g., asthma exacerbation)
    g. Intra-articular steroid injections
    h. Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with SD or an ongoing OR. In such situations, IMP treatment should be interrupted for the duration of immunosuppressive therapy.

    **Prior or concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).*

Questions regarding eligibility criteria must be addressed and resolved by the Investigator in consultation with the Sponsor's Medical Monitor(s) prior to randomization.

5 INVESTIGATIONAL MEDICINAL PRODUCT AND COMPARATORS

5.1 Investigational Medicinal Products

The Investigational Medicinal Products (IMPs) are Sym004, futuximab drug product, and modotuximab drug product.

Sym004 is a 1:1 mixture of two chimeric mAbs, futuximab and modotuximab, which bind specifically to 2 non-overlapping epitopes of the EGFR.

In advance of study start, the Sponsor (or designee) will provide labeled supplies of IMPs to the site pharmacy. Instructions for handling, administration, and disposal will be provided in the IMP Manual and are summarized below.

5.1.1 Formulations

Sym004, futuximab, and modotuximab are each clear to opalescent, colorless to slightly yellow, liquid formulations for IV infusion. Vialed supplies will be provided by the Sponsor with the following volume, concentration, and total content:

- Sym004
    - Nominal fill volume of 20 mL
    - At a concentration of 25 mg/mL for a total vial content of 500 mg
- Futuximab
    - Nominal fill volume of 10 mL
    - At a concentration of 25 mg/mL for a total vial content of 250 mg
- Modotuximab
    - Nominal fill volume of 10 mL
    - At a concentration of 25 mg/mL for a total vial content of 250 mg

5.1.2 Formulation Excipients

Formulation excipients of Sym004, futuximab, and modotuximab include:

- L-Histadine
- L-Histadine monohydrochloride monohydrate
- Trehalose dihydrate
- Tween (polysorbate) 20

5.2 Storage and Handling of IMPs

Unused vials of IMPs must be stored refrigerated between 2° C to 8° C (36 to 46º F) in an access-controlled secure location. IMPs may not be frozen. There is no evidence that ultraviolet (UV) light exposure affects the IMPs, but as a precaution vials should be stored protected from light in the carton until use.

The site will be required to maintain a temperature log documenting IMP storage conditions. The temperature must be logged and evaluated at minimum on all working days.

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor (or designee) and the use of IMP interrupted until authorization for its continued use has been given.

All handling, storage and preparation of IMPs should take place at the site pharmacy. IMPs may be accessed only by the Investigator, a member of the Investigator's staff specifically authorized by the Investigator, or a pharmacist, as appropriate. The site must ensure that IMPs are accessible to authorized personnel only.

5.3 Stability of IMPs

Long-term stability of IMPs is being assessed on an ongoing basis and expiry will be updated as data accrue. The stability of the IMPs will be monitored for at least the duration of the clinical trial.

When diluted for use, the IMPs have been found to be stable at room temperature and should be administered within an 8-hour time window (**Section 5.8**) *(see the IB and the IMP Manual for additional information).*

5.4 Labeling of IMPs

Vials of IMPs will be open-label; label text will be in local language and in accordance with applicable local regulatory requirements. Each vial will be uniquely numbered for allocation, dispensing, and traceability purposes.

5.5 Packaging of IMPs

IMPs will be packed in cartons containing multiple vials. The vial number range in each carton will be detailed on the carton label.

5.6 Administration of IMPs

IMPs will be administered by IV infusion. An appropriate dose based on the patient's body weight is to be diluted with commercially available 0.9% Sodium Chloride Injection, USP or local equivalent.

During this trial, IMPs are to be administered once weekly (Q1W) ± 2 days. Four (4) weeks (28 days) equals one dosing cycle as follows:

- Sym004 (9/6 mg/kg)
    - 9 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min)
    - 6 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min)
- Futuximab (4.5/3 mg/kg)

- 4.5 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min)
- 3 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min)

- Modotuximab (4.5/3 mg/kg)
  - 4.5 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min)
  - 3 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min)

5.7 Dose Calculation

The dose to be administered will be multiplied by the patient's weight in kilograms to arrive at the total dose to be delivered. In situations where this calculation results in a value with an unwieldy number of decimal places, it is permissible to round the value to the nearest "tenth". As a convention, values > 5 should be "rounded" to the next higher number.

Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institutional procedures) as measured at the beginning of each dosing cycle (CxD1). Adjustments may be made in the event of lesser incremental changes in weight and/or more frequently at the site's discretion.

Dosing information will be recorded on the appropriate Accountability Form in use. This inventory will be maintained throughout the duration of the trial and will be periodically reviewed by a representative of the Sponsor.

5.8 Dose Preparation

All handling and preparation of IMPs should take place at the pharmacy of each trial site. The Investigator is responsible for informing the pharmacy of the dose to be administered based on the patient's body weight as measured at the beginning of each dosing cycle.

IMP should be administered by the study staff as soon as possible following preparation, within 8 hours, and considering:

- The total volume of IMP to be delivered will be withdrawn from the IMP vial(s) and added to a prefilled IV bag containing 0.9 % Sodium Chloride Injection, USP or local equivalent (following removal of an appropriate volume of saline, such that the final volume to be infused equals 500 mL for C1D1 loading dose infusions and 250 mL for subsequent infusions)
- The IV bag containing the diluted IMP solution to be administered should be gently inverted to ensure that the material is well mixed.
- Infusion sets must contain an in-line filter (0.22 micron pore size)

5.9 Accountability

The Investigator acknowledges that IMP supplies are investigational and, as such, must be used strictly in accordance with the protocol and only under the supervision of the PI. IMPs will not be sent to the site until all required regulatory documents, including IRB or EC approval, are received by the Sponsor or its designee.

The Investigator and site staff are responsible for maintaining an accurate inventory and accounting of IMPs. Receipt, use, and destruction of IMPs will be recorded on the appropriate Accountability Form in use.

5.9.1 Disposition of Used IMPs

Once IMPs are prepared for delivery and administered, the health care professional will maintain an inventory of all open/used vials. Such residual supplies may be destroyed in an appropriate manner according to institutional policy.

Note: **The Sponsor authorizes no other use of IMP intended for use in this trial.** The Investigator (or designee) will be responsible for the appropriate handling and disposition of residual IMP in partially used vials.

5.9.2 Unused IMPs

Unused study materials MUST be returned to the Sponsor (or designee) upon expiry or at the conclusion of the site's participation in the trial, unless otherwise authorized in writing.

5.9.3 Destruction of IMPs

No unused IMPs may be destroyed or discarded at the site without the written authorization of the Sponsor (or designee). The destruction of IMP materials must be carefully documented per instructions outlined in the IMP Manual. Disposition records must be available for review by a representative of the Sponsor.

6 EXPERIMENTAL PLAN

6.1 Design Elements

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

6.2 Projected Recruitment Period and Duration of this Trial

6.2.1 Recruitment Period

As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted. Previous recruitment projections were as follows:

It is anticipated that enrollment to this study will be completed in approximately 6 months.

- Anticipated date of randomization of first patient: Q3 2018
- Anticipated date of randomization of last patient: Q4 2018

6.2.2 Trial Duration

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the primary, secondary, and exploratory objectives as previously described are no longer applicable. Planned efficacy analyses, as well as planned specialty analyses (including ADA as well as exploratory PK and PD analyses) will not be performed. Only clinical safety-related analyses will be conducted; data cut-off will occur and safety analyses will be performed at the end of trial.

Data Cut-off for Primary Analysis: When the required number of evaluable patients (18 patients per Arm) have been treated for a minimum of 2 cycles, have received any amount of their assigned IMP during that period, and have either undergone EOC2 imaging studies or have had PD documented by imaging studies prior to the EOC2, the trial objectives will be considered to have been met. That date will be the data cut-off date for the primary analysis.

Patients still in treatment will be given the opportunity to continue receiving Sym004.

Data Collection beyond Primary Analysis: While the Sponsor still needs to collect certain safety-related data to meet its regulatory obligations (AEs, serious adverse events [SAEs], IMP dosing, reason for discontinuation, etc.), the Sponsor may elect to reduce non-safety-related protocol-stipulated assessments, and/or transition patients to an extension/rollover protocol.

End of Trial: The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has been discontinued from study drug.

6.2.3 Trial Closure

As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients will not be enrolled. Once the 2 patients entered to the trial have discontinued treatment and all required safety follow-up has been completed, the trial will be closed. The pre-Amendment 5 trial closure plan detailed below will not be followed.

The Sponsor (or designee) will be in communication with the sites when the target total enrollment for the trial has been attained. Once recruitment is completed, accrual will be closed, and sites will be so notified in writing.

6.3 Patient Prescreening, Screening and Randomization

6.3.1 Prescreening for Mutation Status

After obtaining written informed consent, genomic analysis including evaluation of *RAS, BRAF* V600, and *EGFR*-ECD mutations will be performed on blood samples obtained from each potential patient. Results will guide initial eligibility to determine whether to continue a patient in the trial screening process. Triple-negative (TN) results as defined in the trial eligibility criteria will be required for initial eligibility.

All patients giving informed consent for prescreening will receive a unique prescreening number. The trial site must maintain a prescreening log detailing the results for prescreened patients. This log will list the patient's prescreening number, and whether the patient continues into full screening.

Prescreening activities are generally to be performed within 28 days prior to the first day of dosing (C1D1), however, this period may be extended briefly to allow for receipt of genomic analysis results. Alternatively, collection of samples for genomic analysis may be performed under a separate informed consent form (ICF).

6.3.2 Screening for Trial Eligibility

Once a potential patient has been determined to have TNmCRC, screening assessments will be conducted. The Sponsor (or designee) will be made aware of potential patients for enrollment to track such study-related activities.

Imaging studies may be used to document tumor status at screening if performed within 14 days prior to C1D1. Safety screening activities are to be performed within 14 days prior to C1D1, unless otherwise specified.

6.3.3 Submission of Patient Eligibility Information

Once the patient is screened and identified by the Investigator as meeting the study eligibility criteria, data supporting eligibility must be entered in the study CRF for the Sponsor (or designee) to review. Information including: date written informed consent was obtained, demographics, diagnoses of primary malignancy and metastases, prior CRC treatments with systemic drug therapies including those specified in the protocol inclusion criteria will be required.

6.3.4 Eligibility Confirmation

The designated Eligibility Reviewers will review patient eligibility information provided and confirm eligibility. Upon confirmation, the site may proceed to request the randomized study treatment assignment for the patient.

6.3.5 Randomization

As of Amendment 5: As of the trial discontinuation date (20Dec2018), 5 patients had provided written consent for trial participation; following screening, 2 were determined to be eligible. The first patient was deemed eligible prior to the trial discontinuation date and was randomized to Arm B (futuximab). The second patient was deemed eligible after the trial discontinuation date and although randomized to Arm B (futuximab), per Sponsor decision was enrolled to Arm A to receive Sym004. The pre-Amendment 5 randomization plan detailed below will not be followed.

Eligible patients will be randomized in the ratio of 1:1:1 to Arm A (Sym004), Arm B (futuximab), or Arm C (modotuximab).

Randomization is to be carried out within the 14-day screening window with C1D1 dosing to occur on the day of randomization or within 3 days (72 hours) after randomization.

6.3.6 Patient Identification Code Assignment

Each patient who signed informed consent will be assigned a unique identification code. Identification codes will be assigned in sequential order, and will be concatenated to indicate relevant study information, including at minimum the participating trial site and the patient's order of randomization to the trial.

6.3.7 Screen Failures

A patient found not eligible for the trial after giving informed consent will be considered a screen failure. Patients will be followed for the occurrence of SAEs/AEs during the screening process until such time that it is determined that they will not be participating in this trial.

Re-screening of a patient is allowed using the specified criteria and timing, if felt to be justified by the Investigator.

6.4 Requirements for Patient Observation

All patients will be treated and followed on an outpatient basis and will be evaluated and discharged from the clinic on days of scheduled study visits*, unless hospitalization is required for other reasons or to ensure patient safety.

IMP must be administered under the close supervision of a physician or other qualified study personnel experienced in administration of IV agents, and in an environment where full resuscitation facilities are immediately available. Qualified site medical personnel will carefully monitor IV infusions to assess safety and tolerability. Such personnel must be available to evaluate and treat any AEs, as well as to evaluate whether continued participation of the patient in the study is warranted or advisable.

- Patients will be carefully observed for a minimum of 2 hours following completion of the first administration of IMP (C1D1) for evidence of any treatment-related AE(s), and a minimum of 1 hour following completion of subsequent infusions (C1D8 and thereafter).
- At the end of each infusion, the IV line must remain in place during the observation period to allow for administration of IV drugs, if necessary.

Clinical and laboratory assessments will occur at the frequencies indicated (Section** 7). In the event of an AE, assessment frequencies may be increased, as clinically indicated.*

6.5 Drug Treatment Regimen

6.5.1 Study Start Day

All patients will receive the initial dose of their assigned IMP on Day 1 of Cycle 1 (C1D1).

On the day of the first scheduled administration of IMP, and prior to dosing, the Investigator must assess whether any changes have occurred in the clinical state of the patient since Screening which would exclude the patient from the trial.

6.5.2 Patient Availability

The site should calculate study assessment days as well as sample collection dates and times in advance of scheduling a patient's first day of IMP administration, so as to plan accordingly to avoid assessment or collection requirements during non-routine clinic times such as weekends, holidays, etc.

Given the schedule of IMP administration and study assessments outlined herein, patients must be available each cycle on Days 1, 8, 15, and 22 (± 2 days). In addition, for PK sampling*, patients must be available during C1 on D2 and on D4 (± 1 day), and during C2 on D23 and on D25 (± 1 day).

All patients must be available at the end of cycles to determine whether continuation to the next cycle is feasible based on tolerability, and at the end of even-numbered cycles* for imaging studies to evaluate disease status. These activities may be scheduled on Day 1 of the subsequent cycle, prior to dosing, provided assessment results are received and reviewed in advance of patient treatment.

***As of Amendment 5:** PK sampling has been omitted; the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion until confirmation of PD.

6.5.3 IMP Assignments

Based on randomization assignment, patients will receive one of the following IMPs:

- Arm A: Sym004
- Arm B: futuximab
- Arm C: modotuximab

6.5.4 Administration Details

As of Amendment 5: Two (2) patients screened and determined to be eligible have been treated with IMP. The first patient deemed eligible prior to the trial discontinuation date (20Dec2018) was randomized to Arm B (futuximab) and crossed over to Arm A (Sym004) at the EOC1 per Sponsor decision; the second patient deemed eligible after the trial discontinuation date was randomized to Arm B (futuximab), however per Sponsor decision was enrolled to Arm A to receive Sym004.

With this amendment, the doses of IMP to be delivered remain unchanged; however, the pre-Amendment 5 crossover dose plan as detailed below is no longer in effect.

6.5.4.1 Dose

Doses of IMP to be administered are as follows:

- Arm A
    - Loading dose: 9 mg/kg on C1D1
    - Maintenance doses: 6 mg/kg weekly (± 2 days), beginning on C1D8
- Arm B and Arm C
    - Loading dose: 4.5 mg/kg on C1D1
    - Maintenance doses: 3 mg/kg weekly (± 2 days), beginning on C1D8

Changes in Dose to be Administered: Patients will continue to be treated with IMP at that same dose unless dose reduction is necessary due to the occurrence of an AE(s) warranting such action. Once the dose of any IMP is reduced, there will be no dose reescalation. There will be no intrapatient dose-escalation.

Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institutional procedures) as measured at the beginning of each dosing cycle (CxD1). Adjustments may be made in the event of lesser incremental changes in weight and/or more frequently at the site's discretion.

Crossover Dose of Sym004: At the EOC2, ongoing patients from Arm B and Arm C will be crossed-over from futuximab or modotuximab to Sym004; crossover may occur prior to the EOC2 in the event of early radiographic documentation of PD.

Upon crossover, Sym004 will be administered at the dose level that contains the corresponding dose level of the individual antibody futuximab or modotuximab as was previously being administered (prior to crossover). Therefore, patients receiving futuximab or modotuximab at the dose of 3 mg/kg or the reduced dose of 1.5 mg/kg will crossover to receive Sym004 at the dose of 6 or 3 mg/kg, respectively.

Sym004 treatment may be initiated at least one week after the latest dose of futuximab or modotuximab, unless AEs prevent this according to the protocol retreatment criteria (**Section 6.7**). Dosing of Sym004 may continue until further PD is observed.

6.5.4.2 Route of Administration

IMP will be administered by the IV route, via an indwelling venous access catheter, utilizing a controlled infusion device. Infusion sets must contain an in-line filter (0.22 micron pore size).

The catheter may be placed into a peripheral vein (if accessible); administration via central venous catheter or port (if in place) is allowed.

In those instances when IMP administration is associated with PK sampling, and administration is via peripheral IV catheter, infusions will be delivered into the arm contralateral to that from which blood samples for PK analysis are being obtained.

6.5.4.3 Diluent

Commercially available sterile 0.9% Sodium Chloride Injection, USP or local equivalent to be utilized for IV infusion as the diluent.

6.5.4.4 Volume of Infusion

Volumes of infusions are as follows:

- Arm A
  - 9 mg/kg dose will be delivered in a total volume of 500 mL
  - 6 mg/kg (or lower) will be delivered in a total volume of 250 mL
- Arm B and Arm C
  - 4.5 mg/kg dose will be delivered in a total volume of 500 mL
  - 3 mg/kg (or lower) will be delivered in a total volume of 250 mL

6.5.4.5 Duration of Infusion

Durations of infusions are as follows:

- Arm A
  - The initial infusion (9 mg/kg in 500 mL) is to be administered over 1 hour (+ 10 min). The maximum infusion rate of 500 mL/hour should not be exceeded throughout the administration.
  - Subsequent infusions (≤ 6 mg/kg in 250 mL) to be administered over 30 minutes (+10 min), with a maximum infusion rate of 500 mL/hour
- Arm B and Arm C
  - The initial infusion (4.5 mg/kg in 500 mL) is to be administered over 1 hour (+ 10 min). The maximum infusion rate of 500 mL/hour should not be exceeded throughout the administration.
  - Subsequent infusions (≤ 3 mg/kg in 250 mL) to be administered over 30 minutes (+10 min), with a maximum infusion rate of 500 mL/hour

Administration should be at a constant rate using a programmable volumetric infusion pump to ensure accuracy of delivery. Start and stop times of each infusion, and any interruptions in infusion will be recorded on the patient's CRF.

Note: In the event of an IRR, instructions for prolongation of the current and subsequent infusions are provided (**Section 8.2.1**).

6.5.4.6 Schedule

The schedule of dosing is as follows:

- Q1W on Day 1, 8, 15, and 22 of each cycle (± 2 days) (4 weeks [28 days] equals 1 dosing cycle).

A weekly dosing schedule is to be maintained, unless delay is required to allow for amelioration of toxicities (or in the event of scheduling difficulties associated with weekends, holidays, etc.).

6.5.4.7 Premedication for Infusion-Related Reactions

There is an inherent risk for IRRs with the administration of mAbs, therefore premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP. All patients will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen. Recommended premedication doses are provided (**Section 8.1.1.2, Appendix 6**).

Should a patient experience an IRR while in the study, guidelines for premedication following an IRR are provided (**Section 8.1.1.3**). Guidelines for the grading and management of IRRs of all severities are also provided (**Section 8.2.1**, **Appendix 6**).

6.5.4.8 Premedication for Dermatologic AEs

To minimize the risk of dermatologic AEs known to be associated with Sym004, all patients receiving IMP will receive, at minimum during Cycle 1 and 2, minocycline or doxycycline, and will apply topical therapy to the face and chest with a low potency steroid cream, and moisturizing creams/ointments to the hands and body. Use of fragrance-free soaps will be encouraged throughout the treatment period. Guidelines for prophylaxis of dermatologic AEs are provided (see **Section 8.1.2** and **Appendix 7**). Guidelines for grading and management of dermatologic AEs and dose reductions to be implemented in the event of such reactions are also provided (**Appendix 7**).

6.5.4.9 Premedication for Other AEs

In the event of other study-drug associated AEs, patients may be premedicated with standard therapies at the Investigator's discretion to reduce the potential for such reactions in the future. The Sponsor may implement additional mandatory premedication for all patients should a pattern emerge of mild-to-moderate IMP-related AEs (e.g., mucositis, diarrhea) that are amenable to prophylaxis with standard agents.

6.6 Cycle 1

Cycle 1 of IMP will be administered and completed, if tolerated. Any delays in dosing or dose reductions, and the reason for such action must be documented. If an AE is the cause, it must be detailed on the Adverse Events page of the patient's CRF.

6.7 Continued Treatment

Upon completion of Cycle 1, in the absence of unacceptable toxicity, documented PD, or another criterion for treatment discontinuation (**Section 9.1**) patients may continue to receive additional cycles of IMP unless delay is required to allow for amelioration of AEs. Continued administration is at the discretion of the Investigator, provided retreatment guidelines are met.

6.7.1 Retreatment Guidelines

Prior to starting any new cycle, a patient must meet the following criteria:

- ANC $\geq$ 1,000 per mm^3
- Platelets $\geq$ 75,000 per mm^3

- Any ongoing IMP-related AE should NOT meet study discontinuation criteria
- Any ongoing IMP-related AE should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of:
    - Grade 2 alopecia,
    - Grade 2 clinical events that are being adequately controlled with BSC (e.g., nausea, vomiting, diarrhea, fatigue, rash), and
    - Asymptomatic laboratory abnormalities that are considered clinically insignificant, clinically uncomplicated, and/or that are resolving spontaneously or with conventional medical interventions (Grade 2 hypomagnesemia not included as an exception; **Appendix 8**)

Should the above criteria not be met, dosing must be delayed until further evaluation is completed and it is determined that the patient is eligible for continued treatment (for information on dose delays, see **Section 8.2.2**). If a delay is required to allow for amelioration of ongoing AEs, additional cycles should be initiated within approximately 2 weeks after the completion of the previous cycle, if feasible.

6.7.2 Cycle 2

Administration will be at the same dose (unless dose reduction is necessary) and infusion duration established for the patient during the previous cycle, and on the same weekly schedule provided retreatment guidelines are met.

6.7.3 Treatment after Cycle 2

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion. Enrolled patients (2 total) have been either crossed over to receive or are receiving Sym004, and may continue to receive Sym004 until confirmation of PD. The pre-Amendment 5 plan for continued treatment after Cycle 2 as detailed below will not be followed.

Disease assessment and tumor measurements will be conducted at the EOC2. Instructions for continued dosing are as follows:

- Patients assigned to Arm A (Sym004) with a documented OR or SD will continue to receive Sym004; patients with documented PD at the EOC2 will be discontinued from study.
- Patients assigned to Arm B (futuximab) or Arm C (modotuximab) with a documented OR or SD will be crossed-over to receive Sym004; patients with documented PD at the EOC2 (or prior to the EOC2) will be offered the opportunity to crossover to receive Sym004 or will be discontinued from study.

Upon crossover, Sym004 will be administered at the dose level that contains the corresponding dose level of the individual antibody futuximab or modotuximab as was previously being administered (prior to crossover) (**Table 3**). Dosing will be at the same infusion duration established for the patient during the previous cycle, and on the same weekly schedule. Sym004

treatment may be initiated at least one week after the latest dose of futuximab or modotuximab, unless AEs prevent this according to the protocol retreatment criteria. Dosing of Sym004 may continue until further PD is observed.

Table 3: Crossover Dose of Sym004

Previous Futuximab or Modotuximab Dose	Crossover Dose of Sym004
3 mg/kg	6 mg/kg
1.5 mg/kg	3.0 mg/kg

Abbreviations (in alphabetical order): kg, kilogram; mg, milligram

6.8 Duration of Study Follow-Up

Once a criterion for treatment discontinuation is met (**Section 9.1**), every effort will be made to conduct follow-up assessments as detailed below.

For patients continuing to another therapy, the expectation is that Investigators will show due diligence in obtaining adequate follow-up for this study, as indicated. In the event of ongoing AEs, Investigators will do their best to continue patient follow-up, based on both patient availability and Investigator ability to determine the etiology of noted AEs within the context of initiation of any new therapy (i.e., whether the finding is due to IMP or due to the other therapy).

- EOT evaluations will be conducted within approximately 7 to 10 days following the decision to discontinue the patient from treatment with IMP, or before initiation of a new treatment, whichever occurs first.
- 1M FUP evaluations will be conducted approximately 30 days (+7 days) following the last dose of IMP.

  Note: The 1M FUP evaluation should be conducted ≥ 30 days following the last dose of IMP as all patients are to be followed for a minimum of 30 days to monitor for the occurrence of suspected AEs that are both serious and unexpected.

- Long-Term FUP for Safety: If an observed toxicity thought to be related to IMP has not resolved by the 1M FUP evaluation, an additional follow-up AE assessment will be conducted approximately 2 months (may be repeated at 4 months if needed) following the last dose of IMP, if feasible, to confirm that the event has either resolved, returned to baseline status, or been adequately explained and assessed by the Investigator as chronic and/or stable, and that no long-term deleterious effects have become evident*

  **Investigator discretion may be used with respect to the method of contact for this AE assessment. Clinical events may be followed by telephone, e-mail, or in writing; an in-person visit will not be required.*

6.9 Concurrent Treatments and Supportive Care

Therapy for other ongoing medical conditions, as well as palliative and supportive care for the underlying malignancy will be provided prior to and during this trial, as clinically indicated, and in accordance with the standard practices of the institution, except as stipulated by study eligibility criteria (**Section 4.3.2**).

Other therapies allowed during the conduct of this trial include:

1. Prophylaxis for IRRs, Dermatologic AEs, and Other IMP-Related AEs: Premedications for IRRs are mandatory throughout the study. Premedications for dermatologic AEs are mandatory during Cycles 1 and 2, and as indicated thereafter based on the occurrence of related AEs. Premedication for other patient-specific IMP-related reactions may be implemented as indicated at the Investigator's discretion.

2. Treatment of AEs or Concurrent Diseases: Instructions for management of hypomagnesemia are provided (**Appendix 8**). Clinical judgment should be used in the treatment of any other treatment-related AEs or concurrent diseases/conditions that require management during the study and follow-up period.

3. Blood Products and Growth Factors: Blood products and hematopoietic growth factor use is allowed, as clinically indicated.

4. Radiotherapy: Radiotherapy for pain control against non-target lesions, provided it does not substantially influence bone marrow function is allowed.

5. Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions are allowed, provided the patient is on a stable dose for at least 2 months prior to study start and remains on the stable dose while receiving study treatment.
6. Immunosuppressive or systemic hormonal therapy not exceeding 10 mg daily prednisone equivalent is allowed, see **Section 4.3.2** for additional details.

Information on all concomitant therapies administered, as well as other interventions or procedures occurring during the trial period, must be recorded on the appropriate page of the patient's CRF.

7 STUDY ASSESSMENTS

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the original trial design is no longer applicable. Only clinical safety-related evaluations will be conducted. The visit schedule for the treatment period will apply as specified below, with indicated exceptions. Once IMP has been discontinued, an EOT visit will be performed within 7 to 10 days from the decision to withdraw treatment, and a 1M FUP visit will be performed 30 days (+7 days) following the last dose.

The pre-Amendment 5 study assessment schedule was as follows:

All patients will be evaluated by clinical, laboratory, and other diagnostic assessments throughout the study. All efforts should be made to perform assessments as close as possible to the scheduled timepoints. The projection of visit days within each cycle should be made from Day 1 of the respective cycle.

Visit windows are provided below. Study assessments are to be performed as follows:

- Genomic analysis by *Guardant360* (required for eligibility at prescreening) is to be performed within 28 days prior to first administration of IMP; this window may be extended to allow for receipt of analysis result (**Section 7.3.1**)
- Screening disease imaging studies may be used to document tumor status if performed within 14 days prior to first administration of IMP.
- Screening safety evaluations are to be performed within 14 days prior to first administration of IMP, unless otherwise specified (for exceptions see **Section 7.1.1**, **Section 7.2.7.6**, **Section 7.3**).
- The day of first administration of IMP will be considered Day 1 of study.
- On-study evaluations (including laboratory assessments; beginning at C1D1) are to be performed on or about the indicated visit day (i.e., ± 2 working days). A slightly longer allowance for routine assessments is permissible in the event of scheduling difficulties associated with weekends, holidays, etc.
- End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, provided results are available prior to dosing.
- EOT* evaluations are to be performed within approximately 7 to 10 days following the decision to discontinue treatment, or before initiation of a new treatment, whichever occurs first.
- 1M FUP* evaluations are to be performed approximately 30 days (+7 days) following the last dose of IMP (i.e., as all patients are to be followed for a minimum of 30 days after IMP discontinuation to monitor for the occurrence of AEs).

  **When a patient discontinues treatment with IMP, for any reason, every effort will be made to collect routine EOT evaluations as well as subsequent 1M FUP evaluations, per protocol, until all protocol-specified assessments have been conducted.*

If during the study, significant changes in clinical or laboratory findings are noted, additional monitoring or on-study assessments may be undertaken by the Investigator, or requested by the Sponsor (or designee), to determine both the relevance of the finding(s) and the duration of the event(s).

Refer to **Appendix 9** and **Appendix 10** for the maximum total blood collection volumes and the schedule of assessments, respectively.

7.1 Consent and Medical History

7.1.1 Signing of Informed Consent

*(Within 28 days prior to 1st dose; may be extended to allow for receipt of genomic analysis results, or collection of sample for genomic analysis may be performed under a separate ICF; see **Section 7.3.1**)*

- Prior to Screening

Note: All patients must sign an IRB/EC-approved ICF prior to submitting to any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient. A copy of the fully executed ICF will be given to the patient.

7.1.2 Assessment of Eligibility

(Eligibility assessment to be reviewed by Third-Party Investigator Reviewers and the Sponsor's Medical Monitor(s) (or designee) prior to randomization of each patient)

- Prescreening/Screening

7.1.3 Demography

(To include date of birth, sex, race, and ethnicity as allowed in country of study)

- Screening

7.1.4 Past Medical History

(To include prior and ongoing medical illnesses and conditions, prior surgical procedures [not related to the primary diagnosis])

- Screening
- C1D1 (prior to dosing)

7.1.5 History of mCRC

(To include diagnoses of primary malignancy and metastases, prior CRC treatments with surgical procedures, radiation therapies, systemic drug therapies including those specified in the protocol inclusion criteria)

- Screening

7.2 Safety Assessments

(To be performed within 14 days prior to first dose of IMP unless otherwise specified)

7.2.1 Medication and Procedure Surveys

(To include all medications taken other than IMP and all procedures performed during trial. For medications: Include name, indication for use, route of administration, start and stop dates or if ongoing at 1M FUP Visit. For procedures: Include date and reason for procedure. Corresponding illness or condition must appear on the Medical History or Adverse Event pages of the CRF, as appropriate)

- Prior Medication/Procedure Surveys
  - Screening (to assess eligibility)
  - For 14 days prior to first dose
- Concomitant Medication/Procedure Surveys
  - Throughout the study
  - For 30 days following last dose

7.2.2 Adverse Event Reporting

- Starting from signing of informed consent*
- Throughout the study
- For 30 days following last dose
- Long-Term FUP for Safety
  - For AEs ongoing at the 1M FUP
    - For 2 to 4 months following last dose, if events related to IMP persist**#
- As clinically indicated

**To detail any symptoms that may be present prior to first dose. Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.*

***To confirm that events have resolved, returned to baseline status, or been adequately explained*

#Investigator discretion may be used with respect to the method of contact for this AE assessment. Clinical events may be followed by telephone, e-mail, or in writing; an in-person visit will not be required.

7.2.3 Performance Status Evaluation

*(To be assessed by ECOG score; **Appendix 1**)*

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be assessed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.4 Vital Signs

(Vital signs to include temperature, pulse, respiratory rate, and blood pressure)

- Screening
- Cycle 1
  - Day 1
    - Start of infusion (SOI)
    - End of infusion (EOI) (± 5 min)
  - Day 8, 15, and 22 (prior to dosing)
- Each cycle thereafter
  - Day 1, 8, 15, and 22 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

7.2.5 Physical Examination

*(To include measurement of height and weight at screening, and weight** during physical examinations thereafter; assessment of the skin is to be performed during each physical examination)*

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

** Need not be assessed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

*** Dose adjustments may be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institutional procedures]) as measured at the beginning of each dosing cycle. Adjustments may be made in the event of lesser incremental changes in weight and more frequently at the site's discretion.*

7.2.6 Dermatologic Examination

(Timepoints shown are in addition to skin assessments performed as part of scheduled physical examinations; intention is to achieve weekly assessment during the treatment period)

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

- Day 8, 15, and 22 (prior to dosing)

- As clinically indicated

7.2.7 Laboratory Assessments and Pregnancy Test (Local Laboratory)

All routine laboratory analyses will be performed at a laboratory facility local to the trial site. Sponsor (or designee) must be provided with trial site laboratory normal ranges for all required parameters prior to screening of the first patient at the site. Likewise, any change in laboratory normal ranges during the trial should be forwarded to the Sponsor (or designee) promptly during the trial.

Blood samples will be obtained at scheduled visits and analyzed (**Table 4**, **Appendix 10**). Results must be available and assessed prior to dosing, when sampling is scheduled on days of dosing.

Table 4: Schedule of Safety Blood and Urine Analyses

Sample Analysis	Screen	Cycle 1				Cycles Thereafter				EOT	1M FUP
		D1	D8	D15	D22	D1	D8	D15	D22		
Hematology Panel	X	X[1]		X		X				X	X
Biochemistry Panel	X	X[1]		X		X				X	X
Serum Mg, Ca, K*			X		X		X	X	X		
Coagulation Panel	X	X[1]				C2/3 only				X	X
Urinalysis	X	X[1]				C2/3 only				X	X
Pregnancy Test	X	X								X	

Abbreviations (in alphabetical order): Ca, calcium; D, day; EOT, end of treatment; K, potassium; Mg, magnesium;1M FUP, 1-month follow-up

*In addition to magnesium, calcium, and potassium monitoring included with standard biochemistry panel

[1]Does not need to be performed prior to C1D1, if performed during screening ≤7 days from C1D1

In the event of laboratory abnormalities of concern, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated

7.2.7.1 Hematology Panel

(To include complete blood count [CBC] with red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential, ANC, and platelet count)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
  - Day 15 (prior to dosing)
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

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

7.2.7.2 Biochemistry Panel

(Fasting not required; to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen, creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
  - Day 15 (prior to dosing)
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of significant serum chemistry abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. CS electrolyte abnormalities should be corrected prior to dosing.*

7.2.7.3 Serum Magnesium, Calcium, and Potassium

(Timepoints shown are in addition to testing performed as part of scheduled biochemistry panels; intention is to achieve weekly magnesium, calcium, and potassium testing during the treatment period)

- Screening
- Cycle 1
  - Day 8 and 22 (prior to dosing)
- Each cycle thereafter
  - Day 8, 15, and 22 (prior to dosing)
- As clinically indicated*

** An ECG should be performed in the event of ≥ Grade 3 hypomagnesemia and if otherwise clinically indicated.*

7.2.7.4 Coagulation Panel

(To include partial thromboplastin time [PTT] or activated PTT [aPTT], prothrombin time [PT], international normalized ratio [INR])

- Screening
- Cycle 1

  - Day 1 (within ≤ 7 working days prior to dosing)*
- Cycle 2 and 3
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.7.5 Urinalysis

(Multipanel chemical test strips are acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocytes, nitrite, bilirubin, urobilinogen, and blood. Microscopic examination of sediment, if clinically indicated, to include assessment of cells [WBC and RBC] per high power field and casts)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Cycle 2 and 3
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.7.6 Pregnancy Testing

(Beta-human chorionic gonadotropin [β-hCG] in WOCBP; serum at screening, serum or urine thereafter; negative test must be confirmed within 2 working days prior to first dose of IMP)

- Screening
- Cycle 1
  - Day 1 (within ≤ 2 working days prior to dosing)
- EOT
- As clinically indicated (frequency may be increased based on local requirements)

7.2.8 Electrocardiogram (ECG)

(To include standard 12-lead ECG with measurement of PR interval, QRS duration, QT interval, and QTc interval [msec], as well as heart rate)

(To be evaluated locally; ECGs should be performed using the same calibrated instrument at each study center, and should be conducted after the patient has been supine (or semi-recumbent) for ≥ 10 minutes.)

(Patients with a QTc ≥ 500 msec should not be treated; dosing should be delayed.)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Cycle 2 and 3
  - Day 1 (prior to dosing)
- EOT
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. An ECG should be performed in the event of ≥ Grade 3 hypomagnesemia.*

When evaluating QTc interval, baseline should be considered the ECG immediate preceding dosing on the day of assessment.

7.3 Specialty Assessments

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related evaluations will be conducted. Of the Specialty Assessments detailed below, ADA and samples for exploratory PK and PD assessments (in peripheral blood, skin biopsies, and tumor biopsies) will not be collected. Genomic samples for eligibility assessment were obtained at prescreening and analyzed; however post-dosing genomic samples will not be collected.

Note: Samples for ADA and samples for exploratory PK and PD assessments, if collected prior to implementation of this amendment, will not be analyzed and will be destroyed.

The pre-Amendment 5 specialty assessments were as follows:

Laboratory analyses detailed below will be performed at centralized Specialty Laboratory facilities. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites; retention time for specimens will be specified therein. Blood samples, skin biopsies, and tumor biopsies will be taken according to the schedule shown (**Table 5**; **Appendix 10**).

Every effort will be made to collect samples at the timepoints specified. All analyses will be related to and used only with the data collected in the present trial or other Sym004-related trials, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

Table 5: Timepoints for Specialty Assessments (Arm A, Arm B, and Arm C)

Sample Time	Cycle 1					Cycle 2			C Thereafter		EOT	1M FUP
	D1	D4 ±24h	D8	D15	D22	D1	D22	D25 ±24h	D1	D15		
ADA (peripheral blood)												
Prior to SOI	X			X		X			Odd # C			
Visit Day											X	X
PK (peripheral blood)												
Prior to SOI	X		X	X	X	X	X		X	X		
EOI (± 10m)	X		X	X	X	X	X		X	X		
6h > EOI (± 1h)	X						X					
24h > EOI (± 8h)	D2						D23					
Visit Day		X						X			X	X
Genomic Analysis (peripheral blood)												
Visit Day	prescreen*							X**			X***	
Pharmacodynamic Analyses (after confirmation of eligibility)												
Peripheral blood	screening/ pre-C1D1							X**,^			X***	
Skin biopsy	screening/ pre-C1D1					EOC1^		X**,^				
Tumor biopsy	screening/ pre-C1D1							X**,^				

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, cycle(s); D, day; EOI, end of infusion; EOT, end of treatment; h, hour; m, minutes; 1M FUP, 1-month follow-up; SOI, start of infusion

*required at prescreening for eligibility
**preferred day of sampling; coincides with "prior to crossover" for patients in Arm B and Arm C
***EOT with Sym004; need not be repeated if patient is discontinuing at the EOC2
^ End of Cycle assessment may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle prior to dosing

As of Amendment 5: All specialty assessments have been omitted (effective 20Dec2018) with the exception of prescreening genomic sampling for eligibility assessment (*).

7.3.1 Immunogenicity Assessment (Specialty Laboratory)

As of Amendment 5: Immunogenicity assessments have been omitted. Immunogenicity assessments were initially planned as follows:

(To assess for formation of ADA; serum to be isolated)

(All samples must be taken prior to the IMP infusion of that visit. If a collected serum sample is inadequate or insufficient for ADA analysis, analysis may be done using serum from a PK sample from the same timepoint, if available)

- Cycle 1
  - Day 1 (prior to dosing)
  - Day 15 (prior to dosing)
- Cycle 2
  - Day 1 (prior to dosing)
- Odd numbered cycles thereafter

- Day 1 (prior to dosing)

- EOT
- 1M FUP

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints.

7.3.2 Exploratory Pharmacokinetic Assessment (Specialty Laboratory)

As of Amendment 5: Exploratory PK assessments have been omitted. Exploratory PK assessments were initially planned as follows:

(To support determination of the AUC_{inf}, $AUC_{0\text{-}168h}$, $t_{½}$, CL, CL_{ss}, V_d, C_{trough} (SOI) and C_{max} (EOI) concentrations for Sym004, futuximab and modotuximab for exploratory purposes. Data will also enable population PK modeling for further PK characterization; serum to be isolated)

(No additional samples will be collected without formal amendment to this protocol. If a collected serum sample is inadequate or insufficient for PK analysis, the analysis may be done using serum from an ADA sample from the same timepoint, if available)

(If no infusion is planned on a sampling day, the "SOI" sample should be taken during the visit. The exact time point of PK sampling should be noted in the CRF. In case no dosing is planned for C2D22, the samples for the PK profile at EOI and 6 hours after EOI, D23, and D25 should be skipped.)

(In case of crossover from futuximab or modotuximab to Sym004 before EOC2, sampling should continue according to the schedule outlined.)

- Cycle 1
  - Day 1
    - SOI
    - EOI
    - 6 hours after EOI
  - Day 2 (24 hours after EOI)
  - Day 4 (± 24 hours)
  - Day 8 (prior to dosing and at the EOI)
  - Day 15 (prior to dosing and at the EOI)
  - Day 22 (prior to dosing and at the EOI)
- Cycle 2
  - Day 1 (prior to dosing and at the EOI)
  - Day 22
    - SOI
    - EOI
    - 6 hours after EOI
  - Day 23 (24 hours after EOI)
  - Day 25 (± 24 hours)
  - Day 29 (EOC2 or equivalent to C3D1 SOI for patients continuing on Sym004)
- Cycles thereafter (patients continuing on or crossing over to Sym004)

  - Day 1 (prior to dosing and at the EOI)
  - Day 15 (prior to dosing and at the EOI)

- EOT
- 1M FUP

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints.

7.3.3 Genomic Analysis in Peripheral Blood (Specialty Laboratory)

As of Amendment 5: Genomic assessments have been omitted with the exception of prescreening genomic sampling for eligibility assessment (*). Genomic assessments were initially planned as follows:

(To be performed at prescreening for eligibility determination; within 28 days prior to first dose of IMP; may be extended to allow for receipt of genomic analysis results. Peripheral blood to be collected)

- Prescreening (for eligibility)*
- EOC2
  - Day 25 (± 24 hours) *(coincides with PK sampling and pharmacodynamic sampling for all patients and "prior to crossover" for patients in Arm B and Arm C)*
- EOT with Sym004 *(need not be repeated if patient is discontinuing at the EOC2)*
- At the time of radiographically confirmed PD if different from the above

Note: Whole blood (~ 2 × 10 mL) to be collected at each timepoint (plus additional ~ 2 × 10 mL at prescreening to be stored for assay validation purposes); for assessment of ctDNA by *Guardant360*; where blood sample is to be drawn on the day of biopsy (skin; tumor if performed), blood collection to occur prior to performing biopsy procedure(s)

7.3.4 Pharmacodynamic Analyses (Specialty Laboratory)

As of Amendment 5: Pharmacodynamic assessments (including collection of peripheral blood, skin biopsies, and tumor biopsies) have been omitted. Pharmacodynamic assessments were initially planned as follows:

(To be performed after eligibility has been confirmed)

The purpose of pharmacodynamic assessments is to develop an approach for the identification and validation of biomarkers that may predict which patients are likely to respond to Sym004, and that may change with the possible development of acquired resistance.

Analysis may include biomarkers that are unknown or have not been included in the scientific hypotheses of this trial, but that, during the collection of data from this trial, may emerge as indicators related to Sym004 safety, efficacy, or mechanism of action.

All analyses will be related to and used only in connection with the data collected in the present trial and the development of Sym004. The identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

Residuals from samples collected will be stored for up to 15 years after completion of the trial, where after all samples will be destroyed.

7.3.4.1 Peripheral Blood

(Samples will be assessed for serum proteins and other potential biomarkers)

- Screening (after confirmation of eligibility)*
- EOC2**
    - Day 25 (± 24 hours) *(preferred day of sampling; coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arm B and Arm C)*
- EOT with Sym004 (need not be repeated if patient is discontinuing at the EOC2)
- At the time of radiographically confirmed PD if different from the above

**Screening sampling may be conducted at any time prior to C1D1, including on C1D1 prior to dosing.*
***End of Cycle sampling may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*

Note: Whole blood (~ 1 × 20 mL) to be collected at each timepoint; where blood sample is to be drawn on the day of biopsy (skin; tumor if performed), blood collection to occur prior to performing biopsy procedure(s).

7.3.4.2 Skin Biopsies

(Biopsy specimens to be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. Skin biopsies are requested from a rash-free area)

(Samples will be assessed for various parameters, which may include but are not limited to EGFR expression and downstream signaling, markers(s) of proliferation, genomic alterations, etc.)

- Screening (after confirmation of eligibility)*
- EOC1**
- EOC2**
    - Day 25 (± 24 hours) *(preferred day of sampling; coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arm B and Arm C)*

**Screening sampling may be conducted at any time prior to C1D1, including on C1D1 prior to dosing.*
***End of Cycle sampling may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*

Note: Procedure to be performed after collecting blood sample for pharmacodynamic analyses.

7.3.4.3 Tumor Biopsies

(Samples will be assessed for various parameters, which may include but are not limited to EGFR expression and downstream signaling, markers(s) of proliferation, genomic alterations, etc.) Tissue obtained will be cultured in vitro in order to derive primary tumor and non-tumor cell lines. Selected tumor tissue will also be used for engraftment in immuno-compromised mice. Once the tumor is established, it will be expanded by engrafting in multiple mouse

recipients, followed by cryopreservation to be used for subsequent biomarker, genotyping, and preclinical drug evaluation studies by the Sponsor.

- Screening (after confirmation of eligibility)*
- EOC2**
    - Day 25 (± 24 hours) *(preferred day of sampling; coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arm B and Arm C)*

**Screening sampling may be conducted at any time prior to C1D1, including on C1D1 prior to dosing.*
***End of Cycle sampling may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*

Note: Tumor tissue for fresh/frozen cells to be collected at each timepoint; procedure to be performed after collecting blood samples for genomic and pharmacodynamic analyses.

Tumor biopsies to include core samples (if feasible, 3 at screening, 2 at EOC2) of a locally recurrent or metastatic lesion; to be performed with minimal morbidity to the patient by a percutaneous core needle biopsy either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy.

Biopsy specimens will be obtained using standard sterile surgical techniques and handled as directed. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

7.4 Disease Assessments

7.4.1 Diagnostic Imaging for Tumor Measurements (Local Assessment)

(Imaging studies may be used to document tumor status at screening if performed <u>within</u> 14 days prior to first dose of IMP)

To include diagnostic imaging by CT or MRI of the chest, abdomen and pelvis, and other sites as indicated based on suspected tumor location and clinical judgment to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

The same method(s) of disease evaluation and the same technique should be used throughout the study. Additional imaging (such as bone scan) must be performed when other areas of disease are suspected.

For all imaging timepoints, the following will be recorded as per RECIST v1.1: target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; non-target lesions including size, location, and type; any new lesions noted during trial, including size, location, and type (nodal/non-nodal).

- Screening
- **<u>As of Amendment 5</u>:** frequency per either institutional guidelines or Investigator discretion until confirmation of PD

Patients receiving Sym004 with confirmed PD will be discontinued from further treatment so that alternative management of their malignancy may be considered. Patients receiving

futuximab or modotuximab with confirmed PD will be offered the opportunity to crossover to receive Sym004 or will be discontinued from further treatment so that alternative management of their malignancy may be considered.

Once PD is documented and treatment is discontinued and/or another therapeutic intervention is initiated, no further disease assessments will be required.

Imaging data (imaging studies and derived assessments) will be stored according to usual practice by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer.

7.4.2 Response Assessment (Local Assessment)

(To be assessed by the Investigator or qualified designee as per RECIST v1.1; to be noted at each evaluation point as CR, PR, SD, PD, or Not Evaluable [NE] for patient management purposes and to make decisions on continued study treatment)

- **As of Amendment 5:** frequency per either institutional guidelines or Investigator discretion until confirmation of PD

Standard response criteria will be applied (RECIST v1.1, **Appendix 5**).

8 MANAGEMENT OF TOXICITY

Comprehensive assessments of any toxicity experienced by the patient will be performed throughout the course of this study. The Principal Investigator, Sub-Investigator, or designated health professional must be available throughout the course of the study to evaluate and treat any AE(s), as well as to evaluate whether continued participation in the trial is warranted or advisable.

If, at any point during the study, significant changes occur in either the patient's clinical status or laboratory assessments, such changes will be followed until the abnormality either resolves, returns to baseline status, or is adequately explained.

Anticipated toxicities that may be experienced with IMPs are detailed in this protocol (**Section 2.5**, **Section 11**), as well as in the IB. Patients will be evaluated throughout the course of the trial for evidence of acute as well as delayed and/or cumulative toxicities.

If a significant toxicity thought to be related to IMP is experienced at any point during the patient's participation in the study, the Investigator will determine appropriate management, including determining whether that toxicity is such that a change in premedication or a dose modification option such as infusion prolongation, temporary dose delay or dose reduction is warranted. Toxicities where management requires discontinuation from study treatment are detailed in **Section 9.1**.

8.1 Premedication

8.1.1 Premedication for Infusion-Related Reactions

8.1.1.1 Infusion-Related Reactions

There is an inherent risk for IRRs with the administration of mAbs. An IRR is defined as an AE occurring during the IMP infusion and up to 24 hours after the EOI, which is assessed by the Investigator to be related to the infusion. Signs and symptoms of IRRs may include but are not limited to:

- facial flushing and swelling
- rash including urticaria
- headache
- fever
- chills, rigors
- diaphoresis
- tachycardia
- hypotension
- nausea
- dry mouth
- chest/back/abdominal pain/discomfort
- chest and throat tightness
- shortness of breath
- cough, wheeze, stridor
- hypoxia
- bronchospasm

- laryngeal edema
- angioedema
- shock

The risk of an IRR is highest for the first administration of a mAb and diminishes with subsequent infusions.

If an IRR occurs, it should be classified according to the CTCAE v5. Guidelines for grading and management of IRRs of all severities are provided (**Appendix 6**). In each case, the Investigator should use best clinical judgment in managing such reactions. *All ≥ Grade 3 IRRs must be reported promptly to the Sponsor (or designee).*

8.1.1.2 Premedication for Infusion-Related Reactions

Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP.

The following agents are required; recommended doses are provided:

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

The following agents are optional, and may be added to the premedication regimen at any time during the study at the Investigator's discretion; recommended doses are provided:

- Antihistamine (H2 antagonist): equivalent to 50 mg IV ranitidine or 30 mg IV famotidine or equivalent, approximately 0.5 hours prior to the start of Sym004 infusion
- Acetaminophen: 1000 mg IV (where available, or PO), or equivalent, approximately 0.5 hours prior to the start of Sym04 infusion

Note: Doses may be adjusted based on institutional practices. Administration of oral dexamethasone, 10 mg po, (or equivalent) 12 and 6 hours prior to administration of Sym004 is permissible in patients experiencing IRRs or if an increased incidence or severity of IRRs is observed.

8.1.1.3 Premedication for Infusion-Related Reactions (Following an IRR)

For IRRs while in the study, the following premedication instructions are provided (for infusion prolongation instructions following an IRR, see **Section 8.2.1.1**):

- For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedications for subsequent infusions.
- For Grade 4 reactions, not applicable as no further treatment with IMP is allowed.

8.1.2 Premedication for Dermatologic Toxicity

To minimize the risk of dermatologic toxicity, all patients will receive at minimum during Cycle 1 and 2 minocycline or doxycycline, and will apply topical therapy to the face and chest with a low potency steroid cream, and moisturizing creams/ointments to the hands and body. Use of

fragrance-free soaps will be encouraged throughout the treatment period. Guidelines for grading and management of dermatologic AEs of all severities are provided (**Appendix 7**).

8.1.3 Premedication for other IMP-Related Toxicities

Following the first dose, should a patient experience symptoms suggestive of other mild-to-moderate IMP-related reactions (e.g., nausea, vomiting, diarrhea, etc.), the patient may be premedicated with standard therapies to reduce the potential for such reactions in the future.

8.1.4 Institution of Mandatory Premedications

Based on ongoing review of patient safety data, the Sponsor may implement additional mandatory premedication for all patients treated in this study should a pattern emerge of other mild-to-moderate IMP-related reactions (e.g., IRRs and/or any other trends in IMP-related toxicities) that are amenable to prophylaxis with standard agents. Such action will occur following discussions between the Investigator(s) and the Sponsor's Medical Representative(s).

Any medications administered for either prophylaxis or therapy of signs/symptoms related to IMP will be documented on the appropriate page of the CRF.

8.2 Dose Modification Options

8.2.1 Prolongation of Infusion Duration

The option to prolong IMP infusion is most applicable during or following an IRR.

8.2.1.1 Instructions for Infusion Prolongation

For IRRs, the following infusion prolongation instructions are provided (for premedication instructions, see **Section 8.1.1**.

- For Grade 1 reactions, the infusion may be slowed to 50% of the prior rate such that the remaining dose to be delivered is administered 2× longer than the amount of time that was initially scheduled.
- For Grade 2 reactions, the infusion should be interrupted for a minimum of 30 minutes, and at least until there is either amelioration to ≤ Grade 1 severity or return to baseline status. Supportive care should be provided. The infusion should then be restarted at 50% of the prior rate, as described above. Subsequent infusions should be administered at the prolonged rate.
- For Grade 3 reactions, the infusion will be STOPPED and supportive care will be provided. The patient will be either discontinued from treatment, or must receive subsequent treatments at a reduced dose and at a prolonged infusion rate (slowed to 50% of the prior rate or longer).
- For Grade 4 reactions, the infusion will be STOPPED and supportive care will be provided. The patient will be permanently discontinued from treatment.

In all cases, the Investigator should use best clinical judgment in managing such reactions.

All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's CRF.

Note: Any assessments to be performed or samples to be collected (e.g., vital signs, PK) at the end of or following the EOI will still be performed or collected beginning at the delayed EOI timepoint

Guidelines for the grading and management of IRRs of all severities are provided (**Appendix 6**).

8.2.1.2 Treatment Following Infusion Prolongation

To enhance patient safety following an infusion prolongation, subsequent infusions will be administered at the prolonged rate.

8.2.2 Dose Delay

All delays of IMP must be documented on the appropriate page of the patient's CRF.

8.2.2.1 Delay Between Dosing

AEs that warrant dose modification may be managed by delay in dosing, provided they do not meet the criteria for study discontinuation (**Section 9.1**).

In such cases, the period between any 2 scheduled doses may be extended as indicated to allow for amelioration of the toxicity. Such delays will be considered an extension within the current cycle.

8.2.2.2 Retreatment Following Dose Delay

For AEs that are managed by dose delay, dosing may be restarted at the same dose, as clinically indicated. However, administration of IMP may only be restarted upon amelioration to ≤ Grade 1, return to baseline status, or resolution of the observed toxicity, and provided all other retreatment criteria are met (see **Section 6.7.1**).

8.2.3 Dose Reduction

All reductions of IMP dose must be documented on the appropriate page of the patient's CRF. Dose reduction may occur either during treatment cycles, or between cycles, as clinically indicated.

In the event of Grade 3 treatment-related AEs that are self-limiting or manageable by supportive care or other therapy, the patient may continue in the study if there is evidence of OR, SD, or other clinical benefit, but must do so at a reduced dose of IMP. Patients may not be retreated until retreatment criteria are met (see **Section 6.7.1**).

8.2.3.1 Dose Reduction Schedule

If toxicity is to be managed by dose reduction, the IMP dose will be decreased as follows (**Table 6**, **Table 7**):

Table 6: Dose-Reduction of Sym004		
Sym004 Dose	**First Reduction**	**Second Reduction**
6 mg/kg	4.5 mg/kg	3 mg/kg

Abbreviations (in alphabetical order): kg, kilogram; mg, milligram

Note: Dose Reductions for 9 mg/kg loading dose NA; the number of dose reductions allowed is limited to 2 (**Appendix 7**)

Table 7: Dose-Reduction of Futuximab and Modotuximab		
Futuximab or Modotuximab Dose	**First Reduction**	**Second Reduction**
3 mg/kg	1.5 mg/kg	Not applicable

Abbreviations (in alphabetical order): kg, kilogram; mg, milligram;

Note: Dose Reductions for 4.5 mg/kg loading dose NA; the number of dose reductions allowed is limited to 1

8.2.4 Reescalation/Rechallenge Following Dose Reduction

Once a patient has undergone a dose reduction, the patient will continue to be treated at the reduced dose throughout the remainder of their time on study treatment. There is no provision in this study for either reescalation to the previous dose or challenge with a higher dose of IMP.

9 DISCONTINUING PATIENTS FROM STUDY TREATMENT

Every reasonable effort will be made to keep patients in the study; however, if a patient is discontinued from study treatment, every effort will be made by the Investigator to complete and report the reasons for treatment discontinuation as thoroughly as possible. This includes EOT observations, as required by the protocol at the time of treatment discontinuation, or before initiation of a new treatment, whichever comes first, as well as 1M FUP evaluations (**Section 7**). The reason for treatment discontinuation must be clearly documented on the appropriate page of the CRF. A CRF must be completed for any patient who receives any amount of IMP.

9.1 Criteria for Treatment Discontinuation

Patients will be discontinued from further treatment with IMP in the event of any of the following:

1. Progressive Disease: Confirmed radiographically (and evaluated according to RECIST v1.1)

   Note: Patients receiving futuximab or modotuximab with documented PD at the EOC2 (or prior to the EOC2) will be offered the opportunity to crossover to receive Sym004 or will be discontinued from study.

2. Clinical Progression: Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation (i.e., global deterioration characterized by worsening PS, weight loss, and/or worsening clinical symptoms). **Every effort will be made to obtain imaging studies at the time of clinical progression.**

3. Adverse Event including:

   - Hepatotoxicity characterized by:
     - AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor), with
     - total bilirubin ≥ 2 × ULN without initial findings of cholestasis (i.e., serum ALP < 2 × ULN), and
     - No explanation for the above findings such as viral hepatic injury, preexisting or acute liver disease, or another drug or condition capable of causing the observed injury

     Adapted from: Hy's Law. Drug–induced liver injury: premarketing clinical evaluation. Guidance for Industry. U.S. Department of HHS, FDA, CDER, CBER, 2009

   - Any of the following AEs:
     - Need for more than 2 dose reductions (Arm A), or more than 1 dose reduction (Arm B or Arm C)
     - Grade 4 IRR
     - Grade 4 EGFR-associated dermatologic AE
     - Torsade de pointes arrhythmia or other life-threatening arrhythmias
   - Any other AE or SAE considered by the Investigator to require treatment discontinuation

Note: AEs resulting in a patient's permanent discontinuation from study treatment, regardless of seriousness or relationship to IMP, MUST be reported promptly to the Sponsor (or designee).

In the event of Grade 3 treatment-related AEs that are self-limiting or manageable by supportive care or other therapy, the patient may continue in study if there is evidence of response, disease stabilization, or other clinical benefit, but must do so at a reduced dose of IMP (see **Section 8.2.3**). Patients may not be retreated until retreatment criteria are met (see **Section 6.7.1**).

4. Physician Decision: Includes any reason which in the opinion of the Investigator would justify treatment discontinuation (e.g., use/requirement for a non-permitted concomitant medication; requirement for a significant surgical procedure; intercurrent illness which would prevent completion of study-related evaluations)

   Note: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor's Medical Monitor(s). A brief interruption in therapy may be considered.

5. Withdrawal by Patient: Withdrawal of consent and election to discontinue treatment (patients may leave the study at any time for any reason if they wish to do so, without consequence)
6. Protocol Deviation: Significant deviation from the protocol or eligibility criteria; such patients will be considered for discontinuation only following discussion with the Medical Monitor(s)
7. Noncompliance with study procedures
8. Pregnancy
9. Lost to Follow-up
10. Death
11. Study Terminated by the Sponsor

9.2 Replacements

After randomization to the study, no patients will be replaced. Patients NE for antitumor activity assessment, as defined (**Section 3.2**), or patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD, will not be replaced.

9.3 Criteria for Premature Discontinuation of the Trial

This trial may be prematurely discontinued in the event of, but not limited to, any of the following:

- New information leading to an unfavorable benefit-risk profile of the IMP, e.g., due to:
  - Evidence of lack of efficacy of the IMP
  - Occurrence of significant previously unanticipated AEs
  - Clinically significant increase in the frequency or severity of anticipated AEs
  - Other clinically important safety findings

Note: Evidence of lack of efficacy 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 making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of the Sponsor's IMP
- Upon request of Health Authorities

Health Authorities and IRBs/ECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

10 ADVERSE EVENTS

(Instructions for reporting AEs/SAEs apply to any IMP being evaluated in this trial)

10.1 Definitions of Adverse Events

10.1.1 Adverse Event

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

Causality for an AE will be assessed as related or not-related to IMP. Any AE, regardless of causality, that also meets the seriousness criteria, will be reported as an SAE.

10.1.2 Events Not to be Considered as Adverse Events

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

PD will not be captured as an AE as this will be recorded as part of the patient's efficacy evaluation. PD should be reported as an AE if the nature of the PD is different than expected (i.e., signs/symptoms are not typical of PD).

Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.

An abnormal laboratory value or an abnormal physiological test finding (e.g., ECG) need not be reported as an AE unless one of the following applies:

- The Investigator considers the abnormality clinically significant
- The event meets the definition of an SAE
- The event requires an intervention
- The event results in an action taken with IMP (e.g., dose-delay and/or discontinuation)

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

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

10.1.3 Adverse Events of Medical Interest

Not applicable

10.1.4 Serious Adverse Events

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

- **Results in death**

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

- **Is life-threatening**

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

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability/incapacity**

  A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.

- **Is a congenital anomaly/birth defect**
- **Is medically important**

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

10.1.5 Events That Do Not Meet the Definition of Serious Adverse Events

PD will not be captured as an SAE unless the nature of the PD is different than expected (i.e., signs/symptoms that are not typical of PD).

Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.

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

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

Procedures to support the treatment regimen that require hospitalization should not be recorded as SAEs; however, in cases where a procedure results in complications requiring/prolonging hospitalization, this must be recorded and reported as an SAE.

10.2 Adverse Event Recording and Reporting

All AEs will be recorded from signing of informed consent for participation in the trial. The recording period ends 30 days after receiving the final dose of IMP (at the time of the 1M FUP Visit), unless extended FUP is indicated, per the clinical trial protocol.

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

10.2.1 Information to be Provided for Each AE

The Investigator must record all directly observed AEs and all AEs spontaneously reported by the patient. Information regarding the occurrence of AEs should be elicited through open-ended questioning of the patient, review of physical examination findings, and review of laboratory results or other safety information, e.g., ECGs.

All AEs that occur in patients during the AE recording period must be recorded/entered to the AE section of the CRF, whether or not the event is assessed as related to IMP. If the AE is serious, the SAE report forms must also be completed and submitted. Information to be provided for each AE term reported includes:

- **Diagnosis**

  A diagnosis should be recorded, if possible. If no diagnosis is available, signs and symptoms should be recorded instead. For fatal AEs, death is an outcome of the AE. The cause of death (rather than the term "death") should be recorded.

- **Severity**

  The Investigator will use the CTCAE version 5* to describe the severity of an AE. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE (**Appendix 3**):

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

  Changes in severity of AEs will be recorded.

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

  **See <https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50>*

- **Relationship to IMP/Causality**

  The Investigator will attempt to assess causal relationship of the event to the IMP. Relatedness must be assessed and recorded within the initial report (CRF and SAE report form).

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

The causal relationship of an AE to the IMP will be rated using a 2-point causality scale (**Appendix 4**):

- Not-related
- Related

- **Outcome**

  The outcome of the AE must be assessed by the Investigator utilizing one of the following options:

  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Recovering/resolving
  - Not recovered/not resolved
  - Fatal
  - Unknown

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial will be provided.

10.2.2 Required Follow-up for AEs

Appropriate consultation and follow-up evaluations should be carried out until the event either resolves, returns to baseline status, or has been adequately explained and assessed by the Investigator as chronic and/or stable, and that no long-term deleterious effects have become evident.

This follow-up may extend beyond the 1M FUP Visit, to up to 4 months after the EOT if indicated, if the event has not resolved or been adequately explained.

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

10.3 Serious Adverse Event Recording and Reporting

10.3.1 Timeframes for Reporting to the Sponsor

All SAEs occurring at any time from signing of informed consent for participation in the trial and until 30 days after receiving the final dose of IMP (at the time of the 1M FUP Visit) must be recorded on the SAE Report Form and recorded as an SAE in the CRF.

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

In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness.

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

If the Investigator becomes aware of an SAE that occurred after the 1M FUP Visit and finds it to be related to the IMP (possibly-, probably-, or related to the IMP) or trial conduct, it must be recorded and reported to the Sponsor (or designee) as an SAE.

The Investigator should be aware of local reporting regulations to the IRB/EC. The Sponsor (or designee) will either supply the Investigator with the reports, which should be forwarded to the IRB/EC, or report directly to the IRB/EC depending on local regulations.

10.3.2 Safety Reporting to Health Authorities, IRBs/ECs, and Investigators

Reportability of an SAE as a "Suspected Unexpected Serious Adverse Reaction" (SUSAR) will be determined solely by the Sponsor, based on seriousness, causality, and expectedness criteria.

In addition to SUSARs, the Sponsor or designee is responsible for reporting all relevant safety information regarding SUSARs, or other safety developments, to appropriate Health Authorities and central IRBs/ECs, as well as participating Investigators. Reporting of SUSARs to local IRBs/ECs will be handled either by the Sponsor or designee, or the Investigator depending on local regulations.

The timeline for notification of SUSARs is within 7 calendar days for fatal/life-threatening events and within 15 calendar days for all other SUSARs.

10.4 Pregnancy

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

Pregnancies reported in female partners of male trial patients must also be included in the safety database; therefore, a female partner of a male patient on the trial who becomes pregnant will be approached for consent to have the pregnancy followed until term and reported upon to the Sponsor (or designee).

All pregnancies must be followed up every third month and 1-month post-delivery to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate. Elective terminations for non-medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria. Spontaneous abortion must be reported as an SAE.

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

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

11 PRECAUTIONS WHEN DOSING

11.1 Precautions Regarding Procreation

Studies have not been performed to determine whether Sym004, futuximab, or modotuximab affect reproductive function in males or can cause fetal harm. For this reason, men with partners of childbearing potential must use a highly effective method of contraception while receiving IMP. **"A highly effective method of contraception" is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide) or intrauterine device.**

There have been no studies in pregnant females; therefore, it is not known whether Sym004, futuximab, or modotuximab can cause fetal harm when administered to a pregnant woman, or whether they can affect reproductive capacity. For this reason, WOCBP should only be administered IMP when highly effective contraceptive measures have been taken and when pregnancy tests are negative.

WOCBP includes any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is not postmenopausal. Post-menopause is defined as:

- Amenorrhea for ≥ 12 months with no other cause
- Irregular menstrual periods, on HRT, with documented FSH level > 35 mIU/mL

Note: Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, transdermal patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence, or where their partner is sterile (e.g., vasectomy), should be considered of childbearing potential.

Women and men of childbearing potential will be informed as to the unknown risk to procreation while participating in this trial and will be advised that they must use highly effective contraception within 2 weeks prior to the first dose and continuing until 3 months after final administration of IMP. A pregnancy test will be performed on each premenopausal female of childbearing potential within ≤ 2 working days prior to first IMP administration, and again at the end of the final treatment cycle.

11.2 Infusion-Related Reactions

Premedication to reduce the risk of IRRs associated with IMP administration is required. Instructions for premedication (**Section 8.1.1**, **Appendix 6**) and guidelines for treatment and management of IRRs are provided. Facilities and personnel to treat such reactions, if they occur, should be available.

11.3 Dermatologic AEs

The incidence and severity of dermatologic AEs observed in studies of Sym004 are discussed (**Section 2.4.1**). Premedication to reduce the risk of dermatologic AEs associated with IMP administration is required during Cycle 1 and 2.

Patients will be monitored weekly for evidence of dermatologic adverse events.

Recommendations for management of Grade 1 through 3 dermatologic AEs, and for dose delays and reductions in the event of Grade 3 dermatologic AEs are provided (**Appendix 7**). Patients must be withdrawn from IMP treatment in the event of a Grade 4 dermatologic AE.

11.4 Hypomagnesemia, Hypocalcemia, and Hypokalemia

Patients receiving IMP will be monitored weekly for evidence of hypomagnesemia, hypocalcemia, and hypokalemia. Hypomagnesemia should be treated according to the criteria outlined (**Appendix 8**).

11.5 Additional Precautions

There are no known contraindications to the administration of Sym004, futuximab, or modotuximab, however the following additional precautions are provided:

- Lactating women and children: Use in lactating women or in children has not been evaluated. These patients will be excluded from study entry.
- Drug interactions: No formal drug interaction studies have been performed, therefore no specific guidance can be provided about use of concomitant medications.
- Overdose: There is no experience with clinical overdose. If severe reactions occur in patients, IMP should be discontinued and all appropriate supportive medical care should be instituted to ameliorate these potential adverse effects.

12 SAFETY SURVEILLANCE DURING STUDY

12.1 Safety Review

Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the study to make decisions regarding the advisability of continuing accrual. To facilitate this:

- The following will be promptly reported to the Sponsor (or designee):
  - SAEs within 24 hours of Investigator awareness
  - AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to IMP
  - IRRs (≥ Grade 3)
- AEs will be recorded in the CRF in a timely manner following a patient completing (or being discontinued from) a dosing cycle. Each event will be assessed as to grade and causality.
- Dose delays and dose reductions will be recorded in the CRF in a timely manner
- The Investigator will make critical laboratory safety data available in a timely manner.
- Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities, throughout the duration of their time in the study.
- The Investigational Site's staff and the Sponsor's Medical Monitor(s) will maintain contact in the form of email, newsletters, and teleconferences as needed regarding ongoing patient status and any emerging safety concerns

Availability of these data also will enable the Sponsor (or designee) to act promptly in response to safety signals and ensure that governing Health Authorities, as well as Investigators who may be participating at other sites or in other clinical trials of the IMP, are informed of events occurring during the trial.

12.2 Other Safety Surveillance Activities

At least one Medical Monitor will be assigned to review and evaluate relevant clinical/safety information concerning the clinical trial. The responsibilities of the Medical Monitor include, but are not limited to:

- Review of the site's assessment of eligibility
- Consultation with Investigator(s) regarding evaluation of patients to be enrolled to the study, treatment delays, restarts, and/or discontinuations
- Ongoing safety monitoring of all patients being treated in the study
- Evaluation of coding and trending of AEs in conjunction with the Drug Safety physician
- Performing surveillance on potential safety signals in conjunction with the Drug Safety physician
- Evaluating abnormal laboratory values and other relevant safety data, e.g., ECGs

- Providing medical support to the Sponsor in answering questions related to the study protocol
- Updating the Safety Team on trial status

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

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

12.3 Study Safety Committee

Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigator(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns; frequency of teleconferences may fluctuate based on accrual and study activity, as indicated.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Conditions of Testing

In sponsoring this study, it is the intention of the Sponsor to obtain patient safety data for submission to governing Health Authorities. In agreeing to conduct this investigation, the investigative facility agrees to follow all requirements stipulated in this protocol as well as regulations described in the United States (U.S.) Code of Federal Regulations (CFR) and/or by governing Health Authorities concerning:

- Responsibilities of Investigators (in the U.S. Title 21 CFR Part 312)
- Informed Consent of Human Subjects (in the U.S. Title 21 CFR Part 50)
- Institutional Review Boards (in the U.S. Title 21 CFR Part 56)

In addition, the Investigator agrees to perform the study in accordance with the principles of the Declaration of Helsinki and ICH E6(R2) GCP.

13.2 Institutional Review

The Investigator will submit this protocol, any protocol modifications, and the patient ICF to be utilized in this study to the appropriate IRB/EC for review and approval. This committee must operate in accordance with ICH E6(R2) GCP, the U.S. Title 21 CFR Part 56, and/or governing Health Authorities, as appropriate. A letter confirming approval of the protocol and the ICF must be forwarded to the Sponsor (or designee) prior to initiation of this study. The Investigator will not start the study, nor will IMP be shipped to the investigational site, before providing the Sponsor (or designee) with evidence of this approval.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to the IRB/EC. The Investigator will not make any changes in the protocol without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB/EC as required by the IRB/EC. If the study remains in progress for more than the IRB/EC-specified approval period, the Investigator must obtain renewal and re-approval from the IRB/EC where appropriate. Documentation of renewal must be submitted to the Sponsor (or designee). The Investigator will provide notice to the IRB/EC of completion of participation in the study.

13.3 Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the patients entered into the study, including obtaining written informed consent prior to performing any study-related procedures, and informing each patient that the IMP is being used for investigational purposes.

Prior to study start, the Sponsor will provide a sample ICF for modification, as appropriate, by each Investigator. The sample ICF must include all elements required by ICH E6(R2) GCP and must adhere to the IRB/EC requirements and ethical principles that have their origin in the Declaration of Helsinki.

The Investigator's revision to the Sponsor's sample ICF, along with any other written study information to be provided to the patient, must be reviewed and approved by the IRB/EC. A copy of the IRB/EC-approved ICF to be utilized during the study must be submitted to the Sponsor (or designee) prior to study initiation.

Prior to each patient's entry to the study, the Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, its expected duration, and the potential risks associated with participation. All questions about the trial will be answered to the satisfaction of the patient or the patient's legal representative. The patient will be informed of the right to withdraw from the study at any time without consequence, and without having to provide a reason for this decision. Following the discussion, the patient will be asked if they are willing to personally sign and date the ICF. Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study.

It is the responsibility of the Investigator to obtain written informed consent from each patient, thereby attesting that consent was given freely in accordance with ICH E6(R2) GCP, the U.S. Title 21 CFR Part 50, or governing Health Authorities, as appropriate. An Investigator listed on the Form FDA 1572 will then co-sign the ICF. A copy of the signed and dated ICF will be provided to the patient. The original executed version must remain in the Investigator's file, per local requirements, and must be available for verification by a representative of the Sponsor (or designee).

13.4 Conditions for Modifying or Terminating the Study

13.4.1 Modification of the Study Protocol

The study is to be conducted as described in this protocol. Departures from either the protocol eligibility criteria or the experimental plan, as outlined herein, will not be allowed. No protocol waivers will be granted.

If modifications in the experimental design, dosages, assessments, patient selection, etc. of the protocol are indicated or required, such changes will only be instituted following consultation between the Sponsor (or designee) and Investigator and will be accomplished through formal amendment(s) to this protocol and approval by the appropriate regulatory authority (as indicated) and review committees, except where necessary to immediately eliminate apparent hazards to patients.

A modification to the protocol will not be made without the express written approval of the Sponsor (or designee). Any amendment prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) standard operating procedures (SOPs) and will be reported to the appropriate regulatory authority, the appropriate IRB/EC, and made a formal component of the protocol document.

Protocol changes to eliminate an apparent hazard to a trial patient may be implemented by the Investigator immediately. The Investigator must then, without delay, inform the local IRB/EC, and the Sponsor (or designee) will immediately notify local governing Health Authorities.

13.4.2 Modification of the Informed Consent Form

If modifications to the experimental design, dosages, assessments, patient selection, etc. of the protocol are indicated or required, and if such modifications substantially alter the study design or increase the potential risk to patients, the Sponsor (or designee) will prepare a revision to the existing sample ICF for modification, as appropriate, by each Investigator. Any revision to the sample ICF prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) SOPs. Such a revision will be reviewed and approved by the appropriate regulatory authority (as indicated) and IRB/EC.

In addition, all current patients, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent for the modification/risk will be obtained as outlined (**Section 13.3**).

13.4.3 Conditions for Termination of the Study or a Study Site

The Sponsor reserves the right to terminate the study, or terminate a clinical trial site's participation in the study, at any time. Should the Sponsor, the Sponsor's designee, and/or the Investigator(s) discover conditions that indicate the study or a study site should be discontinued, an appropriate procedure for termination will be instituted. Reasons for termination may include, but are not limited to, the following:

- Termination of the Study
    - Safety concerns; incidence and/or severity of AEs in the study that indicate a potential health hazard or unexpected, serious, or unacceptable risk caused by the study treatment
    - Discovery of lack of efficacy
    - Unsatisfactory enrollment across the entirety of the trial
    - Drug supply or manufacturing issues
    - The Sponsor's decision to modify or discontinue development of the IMP
    - A request to discontinue the study by a regulatory authority or Health Authority
- Termination of a Study Site
    - Investigator non-compliance with the protocol, ICH E6(R2) GCP, or regulatory requirements
    - Unsatisfactory enrollment at the site with respect to quantity or quality
    - Incomplete data collection; inaccurate or knowingly false data submission

If terminating the study, the Sponsor and Investigator(s) will ensure that adequate consideration is given to the protection of patients' interests. Further, the governing Health Authority and IRB/EC will be notified in writing and the reason for termination will be stated.

13.5 Trial Registration

The trial will be registered in one or more public trial registries (e.g., ClinicalTrials.gov). The trial results will be posted in the same clinical trial registries as the initial registration in accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

13.6 Insurance and Liability

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

14 INVESTIGATOR RESPONSIBILITIES

14.1 Medical Supervision

An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Parts 50, 56, and 312 and/or by governing Health Authorities, as well as ICH E6(R2) GCP.

Medical supervision for the conduct of this protocol is the responsibility of the Principal Investigator. The Principal Investigator must name all Sub-Investigators and may delegate certain day-to-day activities to such Sub-Investigators, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the design and intent herein. A document outlining the specifics of the delegation will be maintained at the investigational site, in the study files, and will be updated as appropriate.

The Principal Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Principal Investigator is required to ensure compliance with respect to the IMP schedule, visit schedule, and procedures required by the protocol. The Principal Investigator is responsible for ensuring that the study is conducted according to sound medical practices.

14.2 Confidentiality

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol, the patient CRFs, and the IB, are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his/her authority either in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

The submission of this protocol and other necessary documentation to the IRB/EC is expressly permitted; the IRB/EC members have the same obligation of confidentiality.

The Investigator shall consider as confidential, and shall take all necessary measures to ensure that there is no breach of confidentiality, all information accumulated, acquired or deduced during the trial, other than that information to be disclosed to a third party mandated by applicable law.

Note: Any language relating to these issues appearing in the clinical trial agreement will supersede that which is outlined in this section.

14.3 Use of Information

All unpublished information relating to this trial and the IMP is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator must accept that the Sponsor may use information from this trial relating to the development of the IMP, and therefore, may disclose it as required to Investigators, government-licensing authorities, Health Authorities of other governments, investors, and commercial partners as indicated.

14.4 Publications

The Sponsor acknowledges the Investigators' rights to publish the full results of the trial, regardless of the outcome, in accordance with the latest ICMJE recommendations. Publication of a summary of the results of the study is permissible according to the Sponsor and is not inconsistent with the preceding affirmation regarding confidentiality. Scientific dissemination of the results of this study is encouraged. Any formal publication of data collected from the study will be considered a joint publication by the Investigator and the appropriate personnel of the Sponsor or their designees. Authorship will be determined by agreement with the Coordinating Investigator and Study Steering Committee.

The Sponsor retains the right to designate one of the authors or someone else involved to be named as the Coordinating Investigator. The Coordinating Investigator and the Sponsor will decide on the publication strategy. The Coordinating Investigator will have the right to publish and present the results and methods as first or last author of multicenter publications. Co-authorship will be decided by the Sponsor and the Coordinating Investigator and will be limited to persons who have contributed substantially to the trial. The Sponsor will have representation in the list of authors.

Publication is subject to the following conditions:

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

Note: Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that which is outlined in this section.

14.5 Patient Screening Log

A record listing all patients entered into the study, as well as those considered for entry into the study and subsequently excluded, must be maintained by the Investigator. Patients excluded from the study will have the reason for exclusion recorded on the Patient Screening Log (or similar document).

14.6 Drug Dispensing Inventory

Study site personnel will maintain adequate records of the receipt, dispensing, and disposition of all IMP that the Sponsor ships to the site. Records will be maintained either on a form to be provided by the Sponsor or another similar document authorized for use by the Sponsor, and should include appropriate dates, quantities received, quantities dispensed, lot number (or kit number), disposition details, and the identification code of the patient who received the IMP.

The Investigator agrees to administer IMP only to patients under his/her personal supervision. The Investigator will not supply IMP to any person not authorized to receive it.

14.7 Handling and Disposal of IMP

IMP should be stored in a secure location, under the indicated conditions (**Section 5.2**). Information regarding the number of vials utilized for each patient, as well as the dose of IMP administered to the patient, will be recorded on the appropriate drug inventory form.

Periodically throughout and at the conclusion of the study, vials of IMP will be inventoried by a representative of the Sponsor (or designee). At the completion of the study, all unused study materials MUST be returned to the Sponsor (or designee), unless otherwise authorized in writing.

Information regarding the storage, handling, inventory, and disposition of IMP will be provided by the Sponsor (or designee).

14.8 Recording of Data

Clinical trial data for this study will be captured in a CRF. The Investigator agrees to provide all information requested in the CRF in an accurate manner according to instructions provided. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be identified and tracked. Data must be entered into CRFs in a timely fashion.

A CRF is required to be submitted for every patient who receives any amount of IMP. This includes submission of retrievable data on patients who withdraw before completion of the study. Prior to submission, CRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by either the Principal Investigator or a physician Sub-Investigator whose name is listed on the Form FDA 1572 for this study.

All collected data will be entered into a validated database.

14.9 Source Document Requirements

The Investigator will maintain adequate and accurate records for each patient treated with IMP. Source documents including but not limited to hospital, clinic or office charts, laboratory reports, radiology and pathology reports, pharmacy records, study worksheets, anonymized photographs aimed at documenting study-associated clinical findings, and signed ICFs, must completely reflect the nature and extent of the patient's medical care, must be included in the Investigator's files along with patient study records, and must be available for source document verification against entries in the CRF.

Each trial site will permit authorized representatives of the Sponsor and relevant Health Authorities direct access to (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress. The Sponsor (or designee) will check CRF entries against source documents according to the guidelines of ICH E6(R2) GCP. Data not requiring a separate written record, i.e., data which may be recorded directly in the CRF, will be determined before trial start.

The ICF will include a statement by which patients allow the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data in the CRF

(e.g., patient medical files, appointment books, original laboratory records, etc.). The Sponsor (or designee), bound by confidentiality and privacy regulations, will not disclose patient identities or personal medical information.

14.10 Laboratory Reports

Prior to initiation of this study, the Investigator must supply the Sponsor (or designee) with the normal laboratory values for the laboratories to be utilized; specifically, the normal laboratory values for analytes required to be measured, per protocol, are to be supplied.

Laboratory safety evaluations must be performed at the intervals specified. If unexplained laboratory abnormalities occur, corroborative tests will be performed until the laboratory abnormality has resolved, returned to baseline status, and/or adequate explanation of the abnormality has been provided.

Copies of any additional records pertinent to the study (e.g., laboratory data, radiological reports, patient chart summaries, autopsy reports) must be made available to the Sponsor (or designee) or governing Health Authorities, if requested, with due precaution taken to ensure patient confidentiality.

14.11 Record Retention

Regulatory authorities require that the Investigator retain copies of all files pertaining to the study according to local requirements. In addition, the Investigator is responsible for archiving all relevant source documents so that trial data may be compared against source data after completion of the trial, e.g., in case of inspection from authorities. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

If the Investigator relocates, retires, or withdraws for any reason from the study, trial records may be transferred to an acceptable designee, such as another Investigator within the institution. The Sponsor (or designee), as well as the responsible IRB/EC, must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage.

14.12 Monitoring of the Study

The Sponsor has responsibility to governing Health Authorities to take all reasonable steps to ensure the proper conduct of the study with respect to trial ethics, protocol adherence, and data integrity and validity.

This study will be closely monitored by representatives of the Sponsor (and/or designee) throughout its duration. Monitoring will be in the form of periodic personal visits with the Investigator and his/her staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review study progress, Investigator and patient adherence to protocol requirements, and any emergent problems associated with the conduct of the study. The following usually will be assessed during monitoring visits at the site:

- Required regulatory documentation

- Signed ICFs
- Patient accrual and follow-up
- IMP inventory records
- Investigator and patient compliance to the study protocol
- Concomitant therapy usage
- AE documentation
- Data is accurate, complete, and verifiable when compared to source documents

The Investigator and study staff are expected to cooperate with monitors during such visits and provide them with all relevant study documents. The Investigator must give the Sponsor (and/or designee) direct access to all relevant source documents to confirm consistency with the CRF entries. It is important that the Investigator and relevant personnel are available during monitoring visits and possible audits and that sufficient time is devoted to the process.

In addition, the study may be evaluated by Sponsor auditors (and/or designees) and government inspectors who must be allowed access to CRFs, source documents, and other study files. Sponsor reports will be kept confidential. The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, patient authorization to use personally identifiable health information may be required from each patient before research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose, and for how long.

14.13 Patient Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of patients during this clinical study. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP, regulatory, and institutional requirements for the protection of confidentiality of patients.

Coded patient identifiers will be utilized always (including in any publications) when referring to a patient. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor (and/or designee), as well as authorized representatives of the governing Health Authority, to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled into this study. A statement to this effect should be included in the ICF.

14.14 Financing and Insurance

The study will be supported by the Sponsor. Specifics of the financing and insurance coverage will be addressed in the clinical study agreement between the Sponsor and the Investigator or Institution.

15 HANDLING AND PROCESSING OF DATA

15.1 Data Handling

Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).

15.2 Data Review During this Study

Data obtained from the study will be reviewed in a timely manner throughout by the Sponsor (or designee) and Sponsor's Medical Representative(s) to assess safety and the progress of the project.

15.3 Data Processing

A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP.

Once recorded within the CRF, study data will be checked to identify inconsistencies and other data errors, and also will undergo an additional study-specific data review process, as stated above in **Section 15.2.** Data issues will be queried and query resolutions will be documented.

Entry and processing of data other than those directly recorded on CRFs by trial sites (e.g., imports of laboratory results) will follow vendor(s) SOPs. Transfer of such data from vendor(s) to Sponsor (or designee) will be handled according to vendor(s) data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations.

Database Lock will occur upon reaching the predefined data cut-off and completion of Sponsor's (or designee's) quality control procedures and quality assurance procedures.

Portable Document Format (PDF) files of the CRFs will be provided to the Investigator at the end of the trial.

15.4 Clinical Trial Report

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as previously described are no longer applicable. Only clinical safety-related evaluations will be conducted. An abbreviated CTR will be prepared upon completion of the trial rather than the full integrated report described below.

A final integrated clinical/statistical trial report will be prepared upon reaching the predefined data cut-off for primary analysis (i.e., all patients complete their first on-study tumor assessment).

15.5 Compliance with the General Data Protection Regulation

The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This

written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area [EEA]), the parties will enter into the European Commission's standard contractual clauses between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.

16 STATISTICAL ANALYSIS

16.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) that includes a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries analyses will be prepared and finalized prior to database lock.

Further data-driven and exploratory analyses may be defined and performed and presented in the CTR as appropriate.

16.2 Sample Size Considerations

As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients will not be enrolled. Two (2) patients consented prior to the trial discontinuation date and subsequently determined to be eligible have been entered to the study. The pre-Amendment 5 sample size considerations detailed below are no longer valid.

Based on Phase 1 and Phase 2 study results, 37-40% of patients receiving Sym004 9/6 mg/kg weekly treatment are expected to have tumor shrinkage at Week 8 (EOC2). With no knowledge of the anti-cancer effect of futuximab and modotuximab, up to 18 patients per Arm may be enrolled and treated to differentiate the rates of 35% versus 10% using a Simon's 2-stage Minimax design, with a 5% significance level and 80% power, for each of the futuximab and modotuximab Arms. In Stage 1, 11 patients will be enrolled in each Arm and treated. If no more than 1 patient has tumor shrinkage in an Arm, further enrollment will be stopped in that Arm. Otherwise, an additional 7 patients will be enrolled in Stage 2.

A contemporary reference Sym004 Arm will be included in the study to ensure the interpretability of tumor shrinkage data for the Futuximab Arm and Modotuximab Arm.

If either of the Futuximab or Modotuximab Arms continues in Stage 2 or beyond, the Sym004 Arm enrollment will continue.

16.3 Analysis Sets

The efficacy and safety analysis sets are defined as follows:

- As-Treated (AT) Analysis Set: This analysis set includes all patients who took part of any dose of study treatment, will be used as basis for the evaluation of antitumor effects and safety analyses. All analyses using this population will be based on the treatment actually received.
- PK Analysis Set*: All patients in the AT analysis set who receive any amount of their assigned dose of the IMPs, Sym004, futuximab or modotuximab, have a measurable concentration of at least one of the IMPs for at least one timepoint after the first dose, with no significant protocol deviations that may impact the data.

  ***As of Amendment 5:** PK analysis will not be performed, therefore the PK analysis set is no longer applicable.

16.4 Trial Endpoints

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The pre-Amendment 5 efficacy and exploratory endpoints as detailed below are no longer valid and will not be analyzed.

16.4.1 Primary Efficacy Endpoint (omitted as of Amendment 5)

Percentage change from baseline in the sum of the diameter of tumors designated as target lesions, as documented at the EOC2 tumor assessment.

16.4.2 Exploratory Endpoints and Analyses (omitted as of Amendment 5)

16.4.2.1 Pharmacokinetic Endpoints

The PK profile of the IMPs will be derived based on the concentration time curves after the first and the 8th infusion on Cycle 2, Day 22. For patients dosed with Sym004, the serum concentration of futuximab and modotuximab will be measured in separate bioanalytical assays. The Sym004 serum concentration is defined as the sum of futuximab and modotuximab serum concentrations measured in a sample. The bioanalytical assays used for Sym004 assessment will also be applied for measurement of serum concentrations of futuximab and modotuximab in the patients dosed with futuximab drug product and modotuximab drug product, respectively.

For all three IMPs, the C_{max}, C_{EOI}, C_{trough} and T_{max} will be derived from observed data while AUC_{inf}, $AUC_{0\text{-}168h}$, CL, CL_{ss}, Vd, and $T_{½}$ will be estimated using non-compartmental methods and actual time points. For selected infusions during repeated dosing, C_{EOI} and/or C_{trough} (equivalent to the concentration at EOI and SOI, respectively) will be assessed.

Individual curves of serum concentration of the IMPs versus time after the first and 8th infusion will be presented on log- and linear scale for all patients in the PK population. Furthermore, peak and trough serum concentrations for the period from first dose to EOC2 and EOT, before and after cross-over to Sym004 will be presented on a linear scale individual plots as appropriate. In addition, mean concentration time curves will be presented on linear scale using nominal time point by cohort and trial part. All PK endpoints will be listed and summarized by trial part and cohort (**Table 8**).

Table 8: PK Endpoint, Definitions, and Derivations

Symbol	Definition and Derivation
AUC_{inf}	Area under the concentration-time curve from start of infusion to infinity for the first dose
$AUC_{0\text{-}168h}$	Area under the Concentration-Time Curve from Start of Infusion up to 168 hours
CL	Clearance after the first dose
CL_{ss}	Clearance in steady state at the nominal 8th infusion
C_{EOI}	Concentration at the end of infusion
C_{max}	Maximum concentration
C_{trough}	Observed trough concentration (i.e., concentration of IMP measured pre-infusion)
$T_{½}$	Terminal elimination half-life
V_d	Volume of Distribution During the Terminal Phase after the First Dose

16.4.2.2 Modeling of Pharmacokinetic and Pharmacodynamic Data

All data collected in this trial may be used for modeling of PK, tumor size, safety, and biomarker assessments. Preliminary data generated during the trial may be used for exploratory modelling. The final data, i.e., after database lock, will be used for the final model and potentially for cross-trial modelling. These modelling activities will be reported separately from the current trial.

16.5 Statistical Analysis

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only data from clinical safety-related evaluations will be summarized. Since only 2 patients are being treated in the study, the available baseline and safety data for these two patients will be presented as either patient profiles or patient listings. The pre-Amendment 5 full statistical analysis as detailed below will not be performed.

16.5.1 General Specifications

Statistical analyses will be carried out using Statistical Analysis System (SAS®) Version 9.4 or higher.

The data cut-off for primary analysis date will be determined once all patients in the AT analysis set complete their first on-study tumor assessment.

In general, continuous variables will be summarized using descriptive statistics by reporting the number of observations, mean, standard deviation, median, minimum, and maximum; Categorical/discrete variables will be summarized using frequency distributions showing the number and percentage of patients within each category; unless otherwise specified.

Baseline is defined as the last available observation prior to the first administration of study drug on C1D1. If a baseline value is missing, no change from baseline will be calculated.

Unless indicated otherwise, summary statistics will be presented using observed data only. Missing data will not be imputed unless otherwise specified.

Data from all study sites will be pooled in the summaries if more than one site is involved in the study. Study sites will be identified in the data listings.

16.5.2 Patient Disposition and Baseline Characteristics

16.5.2.1 Patient Disposition

Number of patients in each analysis set, reasons for exclusion, withdrawals of patients from study drug and reason, as well as withdrawal from study follow-up, will be summarized using frequency distributions. Randomization and/or stratification errors, if any, will be summarized.

16.5.2.2 Baseline and Disease Characteristics

Patient demographics, baseline and disease characteristics such as age, sex, race, duration of metastatic disease, prior anti-cancer therapies, measurable/non-measurable disease, left or right colon, and ECOG PS, will be presented using descriptive statistics or frequency distributions, as appropriate.

16.5.3 Exposure

Exposure to study drug and the administration profile will be summarized descriptively for each treatment Arm with respect to duration of exposure, number of treatment cycles, cumulative dose, relative dose intensity, and dose modifications.

16.6 Primary Analysis

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned efficacy analyses as detailed below will not be performed.

16.6.1 Efficacy Analysis

Percentage change from baseline in the sum of the diameters of tumors designated as target lesions, as tumor volume documented at the EOC2 tumor assessment will be calculated and plotted by treatment Arm using Waterfall plots. Percent of patients with on-study tumor shrinkage will be presented along with the associated 95% CIs. Magnitude of tumor shrinkage will also be summarized by treatment Arm, as appropriate.

16.7 Secondary Analysis

16.7.1 Safety Analysis

The safety evaluations will focus on AEs and laboratory assessments. All patients included in the AT analysis set will be evaluated by treatment Arm in the safety analysis.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities will be graded according to the CTCAE v5, where applicable. Concomitant medications will be coded according to the World Health Organization (WHO) Medication Dictionary for Concomitant Medication.

All AEs will be summarized (incidence) and listed by the System Organ Class (SOC), preferred term, toxicity/severity grade, and causal relationship to study medication. In addition, separate summaries of SAEs and Grade 3 and 4 AEs will be presented.

Special attention will be paid to dermatologic toxicities, hypomagnesemia, hypocalcemia, hypokalemia, and IRRs.

Hematological and chemistry laboratory parameters will be graded according to the CTCAE v5 criteria, where applicable. Absolute values and changes from baseline will be summarized by cycle. The on-study worst severity grade will also be summarized. In addition, time to event (certain severity of selected laboratory tests), and time to resolution will also be summarized as appropriate.

Further safety analysis details will be provided in the SAP.

16.8 Exploratory Analysis

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned exploratory analyses as detailed below will not be performed.

16.8.1 Exploratory Biomarker and Pharmacodynamic Analyses

Biomarker and pharmacodynamic assessments, to include collection of peripheral blood, skin biopsies, and tumor biopsies, will be conducted in all patients and will evaluate potential predictive and/or prognostic biomarkers of response to treatment, including but not limited to: mutations; gene amplification and altered protein expression of members of the human EGFR family and other receptor tyrosine kinases; and downstream signaling mediators.

Biomarker analyses will be performed according to standard methodologies. Analyses will be described in the SAP.

16.9 Deviations from the Preplanned Statistical Analyses

Any deviation(s) from preplanned statistical analyses defined prior to randomization of the first patient will be described in a protocol amendment and/or in the SAP and/or in the final CTR, as appropriate.

16.10 Interim Analysis

As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned interim analyses as detailed below will not be performed.

Per study design, tumor shrinkage will be evaluated at the end of Stage 1 and Stage 2. No other interim analysis is planned.

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18 APPENDICES

Appendix 1 Performance Status Evaluation

Table 9: Measures of Performance Status

Percent	KARNOFSKY Performance Status Description[1]	Level	Eastern Cooperative Oncology Group (ECOG) Performance Status Description[2]
100	Normal; no complaints, no evidence of disease	0	Normal activity
90	Able to carry on normal activity; minor signs or symptoms of disease		
80	Normal activity with effort; some signs or symptoms of disease	1	Symptoms but ambulatory
70	Cares for self; unable to carry on normal activity or do active work		
60	Requires occasional assistance but is able to care for most needs	2	In bed < 50% of time
50	Requires considerable assistance and frequent medical care		
40	Disabled; requires special care and assistance	3	In bed > 50 % of time
30	Severely disabled; hospitalization is indicated although death is not imminent		
20	Very sick; hospitalization is necessary	4	100 % bedridden
10	Moribund; fatal processes progressing rapidly		
0	Death	5	Death

[1]Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*. 1948;1:634-656.

[2]Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. (CCT) 1982; 5:649-655.

Appendix 2 New York Heart Association Functional Criteria

Table 10: New York Heart Association Functional Criteria	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken discomfort increases.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

Appendix 3 Clinical Adverse Events: Grading Scale

Table 11: Clinical Adverse Event Grading		
Severity	**CTCAE*Grade**	**Definition**
Mild	1	Awareness of symptom, but easily tolerated. Event is usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	Event may be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Event results in temporary disability or incapacity; inability to perform usual activities; requires intervention
Life-threatening	4	Event requires immediate intervention; need for emergency treatment; patient is at risk of death at the time of the event
Fatal	5	Event resulting in the subsequent death of the patient

Note: In those cases where further definition of an event is provided by the CTCAE (v5), please refer to that document for grading and severity information.

* *<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50>*

Appendix 4 Clinical Adverse Events: Determining Relationship to IMP

Table 12: Clinical Adverse Event Attribution
NOT-RELATED
This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) that are not-related to the administration of IMP.
RELATED *(must have first 3)*
This category applies to those AEs, which, after careful medical consideration, are felt to be related to the administration of the IMP. The relationship of an AE to the IMP can be considered related if: • It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues. • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases upon cessation of drug or reduction on dose (if applicable) and appears upon rechallenge.* • It follows a known response pattern to the suspected drug.

Adapted from: Karch FE and Lasagna L. Adverse drug reactions: a critical review. *JAMA*. 1975 Dec 22; 234 (12):1236-1241.

**There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists, e.g., 1) tardive dyskinesia, 2) fixed drug eruptions.*

Appendix 5 Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Table 13: Summary of RECIST v1.1 Guidelines

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response (OR).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST v1.1 criteria.

A. DEFINITIONS

Evaluable for Toxicity: All patients will be evaluable for toxicity from the time of their first treatment with IMP.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

B. DISEASE PARAMETERS

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥10 mm with CT scan, or as ≥10 mm with calipers by clinical examination. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.
If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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 at follow-up, only the short axis will be measured and followed.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion

does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

C. METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: 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 is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline defines measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST v1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST v1.1 measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review later, and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound during the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure using CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate specific antigen (PSA) response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions based on FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- *If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.*
- *If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).*
- *If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing based on the anatomic images, this is not PD.*

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

D. RESPONSE CRITERIA

1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed later by the review panel (or Principal Investigator).

3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* *See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.*
** *Only for non-randomized trials with response as primary endpoint.*
*** *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.*

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Abbreviations (in alphabetical order): CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* *Non-CR/non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials, so to assign this category when no lesions can be measured is not advised.*

Abbreviations (in alphabetical order): CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

E. DURATION OF RESPONSE

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

F. PROGRESSION FREE SURVIVAL

Progression Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Adapted from: 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; 45:229-247.

<*http://www.eortc.be/recist/documents/RECISTGuidelines.pdf* >

Appendix 6 Management of Infusion-Related Reactions

A. Prophylaxis for Infusion-Related Reactions

Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP. All patients must be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen.

Required and optional agents, as well as recommended doses, are provided (**Table 14**).

Table 14: Premedications for Infusion-Related Reactions

Drug Class	Recommended Dose	When to Administer prior to infusion
Required Agents		
Glucocorticoid	equivalent to 80-100 mg IV methylprednisolone	approximately 0.5 to 2 hours
Antihistamine (H1 antagonist)	equivalent to 25-50 mg IV diphenhydramine	approximately 0.5 hours
Optional Agents		
Antihistamine (H2 antagonist)	equivalent to 50 mg IV ranitidine or 30 mg IV famotidine, or equivalent	approximately 0.5 hours
Acetaminophen	1000 mg IV (where available, or PO), or equivalent	approximately 0.5 hours

Abbreviations (in alphabetical order): IV, intravenous; mg, milligram

Note: Doses may be adjusted based on institutional practices. Administration of oral dexamethasone, 10 mg po, (or equivalent) 12 and 6 hours prior to administration of Sym004 is permissible in patients experiencing IRRs or if an increased incidence or severity of IRRs are observed.

For IRRs while in the study, the following premedication instructions are provided:

- For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedications for subsequent infusions.
- For Grade 4 reactions, not applicable as no further treatment with IMP is allowed

B. Grading of Infusion-Related Reactions

The CTCAE v5* definition of IRRs (General Disorders and Administration Site Conditions) is shown below. Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "Infusion-Related Reaction" and any additional terms (including those not listed here) that best describe the event. Those described should be graded as follows (**Table 15**):

Table 15: Grading of Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 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, IV 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.					
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); 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 (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV 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 (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

**See <https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50>*

C. Guidelines for Management of Infusion-Related Reactions

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade ≥ 2 allergic/hypersensitivity reactions. The Sponsor should be contacted immediately if questions arise concerning the grade of the reaction. The following are recommended management guidelines for IRRs associated with IMP administration. In all cases the Investigator should use best clinical judgment in managing such reactions (**Table 16**).

Table 16: Management of Infusion-Related Reactions

Grade 1	• Consider slowing the infusion to 50% of the prior rate • Monitor the patient for worsening condition • If the infusion is extended, administer subsequent infusions at the prolonged rate • Consider additional premedication or adjustment to premedications for subsequent infusions
Grade 2	• Interrupt the infusion for a minimum of 30 minutes • Administer additional pharmacologic therapy (e.g., diphenhydramine, acetaminophen) and appropriate supportive care (e.g., oxygen), as medically indicated • Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to ≤ Grade 1 • Monitor the patient for worsening condition • Administer subsequent infusions at the prolonged rate • Consider additional premedication or adjustment to premedications for subsequent infusions
≥ Grade 3	• Stop the infusion • Administer additional pharmacologic therapy (diphenhydramine, dexamethasone) and appropriate supportive care (e.g., oxygen), as medically indicated • Administer epinephrine or bronchodilators as medically indicated • Hospital admission for observation may be indicated • Do not resume infusion after a ≥ Grade 3 reaction • Patients who have a Grade 3 infusion-related reaction will be either discontinued from treatment, or must receive subsequent treatments at a reduced dose and a prolonged infusion rate (slowed to 50% of the prior rate or longer) • Consider additional premedication or adjustment to premedications for subsequent infusions • Patients who have a > Grade 3 infusion-related reaction will be discontinued from treatment

In the Event of Infusion Prolongation

Any assessments to be performed or samples to be collected (e.g., vital signs, PK) at the end of or following EOI will still be performed or collected beginning at the delayed EOI timepoint.

All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's CRF.

Appendix 7 Management of Dermatologic Adverse Events

A. Prophylaxis for IMP-Related Dermatologic AEs

Patients receiving Sym004, futuximab, or modotuximab are to receive mandatory prophylactic treatments for acneiform rash during Cycle 1 and 2 as described (**Table 17**).

Table 17: Mandatory Premedications for Dermatologic AEs

Treatment	Dose	Start	Stop	Alternatives
Systemic Therapy				
minocycline or doxycycline	1 × 100 mg/day 2 × 100 mg/day	C1D1	EOC2[b]	In case of intolerance • first generation cephalosporin • amoxicillin • erythromycin • limecycline
Topical Therapy				
low potency steroid creams such as: • alclometasone 0.05% • desonide 0.05% • fluocinolone 0.01%	2 × daily on face and chest	C1D1	EOC2	
moisturizer (creams or ointments)	3 × daily to the hands, and after hand washing[c]; 2 × daily on the rest of the body	C1D1	Continue	

Abbreviations (in alphabetical order): C1D1, Cycle 1 Day 1; EOC2, end of Cycle 2; mg, milligram

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 EOC2 at the Investigator's discretion or in the event of CTCAE Grade 2 rash.
c. Use fragrance free soap.

B. Grading and Management of IMP-Related Dermatologic AEs

The incidence and severity of dermatologic AEs observed in studies of Sym004 are discussed (**Section 2.4.1**). Recommendations for management of Grade 1 to Grade 3 dermatologic AEs are provided below (**Table 18**-**Table 23**).

If a patient experiences any Grade 4 dermatologic AE, the patient must be withdrawn from IMP treatment. It is strongly recommended that a dermatologist is consulted in the event of Grade 3 or Grade 4 dermatologic AE.

Table 18: Management of Rash – Sym004, Futuximab, or Modotuximab

CTCAE Grade		Action with IMP	Treatment- Rash
1	Papules and/or pustules covering **<10% BSA**, which may or may not be associated with symptoms of pruritus or tenderness	Continue at the same dose	Topical: Face and Chest Steroid creams of low potency; alclometasone 0.05% or desonide 0.05% or fluocinolone 0.01%; 2×daily Topical: Rest-of-body moisturizers; 2×daily Systemic[1]: minocycline 100 mg/day or doxycycline 200 mg/day; for at least 4 weeks
2	Papules and/or pustules covering **10-30% BSA**, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limited instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose-reduction as outlined in **Table 24** and **Table 25**	Topical: See Grade 1 Systemic[1]: • minocycline 100 mg/day or doxycycline 200 mg/day; for at least 4 weeks • 1 week course of oral steroid: methylprednisolone 4 mg tablets: o Day 1: 2-1-1-2 o Day 2: 1-1-1-2 o Day 3: 1-1-1-1 o Day 4: 1-1-1 o Day 5 1-0-1 o Day 6: 1
3	Papules and/or pustules covering **>30% BSA**, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Delay dose of Sym004, continue skin treatment and re-assess. Refer to **Table 24** and **Table 25** for further guidelines on dose-reduction	Topical: See Grade 1 Systemic[1]: See Grade 2

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events v5

1. Alternatives in case of intolerance: First generation cephalosporins, amoxicillin, erythromycin or limecycline.

If infection is suspected (yellow crusts, purulent discharge, painful skin/nares): Obtain culture and change to oral antibiotic based on sensitivity

Table 19: Management of Xerosis – Sym004, Futuximab, or Modotuximab

CTCAE Grade		Action with IMP	Treatment-Xerosis
1	**<10% BSA** and no associated erythema or pruritus	Continue at the same dose	Topical: Face moisturizing cream or ointment[1]; 2×daily *and* Topical: Body ammonium lactate 6-12% cream; 2×daily
2	**10-30% BSA** associated with erythema or pruritus; limited instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose-reduction as outlined in **Table 24** and **Table 25**	Topical: Face moisturizing cream or ointment[1]; 2×daily *and* Topical: Body ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream; 2×daily
3	**>30% BSA** associated with pruritus; limited self-care ADL	Delay dose of Sym004, continue skin treatment and re-assess. Refer to **Table 24** and **Table 25** for further guidelines on dose-reduction	Topical: Face moisturizing cream or ointment[1]; 2×daily *and* Topical: Body ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream; 2×daily *and* Topical: Eczematous areas topical steroid (e.g., triamcinolone acetonide 0.025% or desonide 0.05% or alclometasone 0.05% or fluticasone propionate 0.05%); 2×daily

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events v5

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

Table 20: Management of Paronychia – Sym004, Futuximab, or Modotuximab

CTCAE Grade		Action with IMP	Treatment-Paronychia
1	Nail fold edema or erythema; disruption of the cuticle	Continue at the same dose	Topical: antibiotics (e.g., clindamycin 1% or erythromycin 1%) *and* vinegar soaks (i.e., soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 min daily
2	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose-reduction as outlined in **Table 24** and **Table 25**	Same as for Grade 1 *and* Topical: silver nitrate application weekly (needs consultation with dermatologist or surgeon) *and* Systemic: bacterial culture, oral antibiotic if infection confirmed
3	Surgical intervention or IV antibiotics indicated; limiting self-care ADL	Delay dose of Sym004, continue skin treatment and re-assess. Refer to **Table 24** and **Table 25** for further guidelines on dose-reduction	Same as for Grade 1 *and* Topical: silver nitrate application weekly (needs consultation with dermatologist or surgeon) *and* consider nail avulsion (needs consultation with dermatologist or surgeon) *and* Systemic: bacterial culture, oral antibiotic if infection confirmed

Abbreviations (in alphabetical order): ADL, activities of daily living; IV, intravenous; CTCAE, Common Terminology Criteria for Adverse Events v5

Table 21: Management of Pruritus – Sym004, Futuximab, or Modotuximab

CTCAE Grade		Action with IMP	Treatment-Pruritus
1	Mild or localized; topical intervention indicated	Continue at the same dose	Topical: steroid (e.g., triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, Fluticasone propionate 0.05%); 2×daily *or* anti-pruritics (e.g., pramoxine 1%, doxepin 5% cream); 2×daily
2	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose-reduction as outlined in **Table 24** and **Table 25**	Same as for Grade 1 *and* Systemic: oral antihistamines (diphenhydramine 25-50 mg; hydroxyzine 25 mg; fexofenadine 60 mg; 3×daily
3	Intense or widespread; constant; limiting self-care, ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	Delay dose of Sym004, continue skin treatment and re-assess. Refer to **Table 24** and **Table 25** for further guidelines on dose-reduction	Same as for Grade 2

Abbreviations (in alphabetical order): ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events v5

Table 22: Management of Photosensitivity – Sym004, Futuximab, or Modotuximab

CTCAE Grade		Action with IMP	Treatment-Photosensitivity
1	Painless erythema and erythema covering **<10% BSA**	Continue at the same dose	Topical: broad spectrum sunscreen with an SPF of at least 15; reapplied every 2 hours or more frequently if swimming or perspiring *and* Systemic: bacterial culture, oral antibiotic if infection confirmed
2	Tender erythema covering **10-30% BSA**	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose-reduction as outlined in **Table 24** and **Table 25**	Same as for Grade 1 *and* Topical: corticosteroids (e.g., triamcinolone acetonide 0.025% or desonide 0.05% or alclometasone 0.05% cream or fluticasone propionate 0.05%); 2×daily
3	Erythema covering **>30% BSA** and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Delay dose of Sym004, continue skin treatment and re-assess. Refer to **Table 24** and **Table 25** for further guidelines on dose-reduction	Same as Grade 2

Abbreviations (in alphabetical order): BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events v5; NSAID, nonsteroidal anti-inflammatory drug; SPF, sun protection factor

Table 23: Management of Fissures – Sym004, Futuximab, or Modotuximab

Treatment Step		Action with IMP	Treatment-Fissures
1	Initiated at first occurrence	No action	Topical: • thick moisturizers of zinc oxide (13-40%) cream • liquid glues of cyanoacrylate to seal cracks
2	If no improvement after 2 weeks from initiation of Step 1	No action	Topical: • thick moisturizers of zinc oxide (13-40%) cream under occlusion at night • salicylic acid 6% cream or ammonium lactate/lactic acid 12%
3	If no improvement after 2 weeks from initiation of Step 2	Delay dose of Sym004 and re-assess. Discuss need for dose-reduction and/or further dose omissions with Sponsor or designee	Continue local treatment as described in Step 2

Prophylaxis for fissures includes careful use of moisturizing creams and/or ointments 3 times a day and after handwashing, using only fragrance-free soaps. Should fissures begin to form, a stepwise approach outlined above should be followed.

If fissures occur which are unresponsive to intensive therapeutic treatment as specified above, Sym004, futuximab, or modotuximab dosing should be delayed. The need for dose-reduction and/or continued dose-delays should be discussed with the Sponsor or designee, if adequate improvement is not seen after the initial dose-delay.

C. Dose Reduction Guidelines for IMP-Related Dermatologic AEs

Dose delay and/or intrapatient dose-reduction(s) will be required upon occurrence of Grade 3 anti-EGFR-associated dermatologic AE, and should be implemented according to the following tables (**Table 24**, **Table 25**):

Table 24: Dose Reduction for Grade 3 Dermatologic AEs - Sym004

Dermatologic AE Grade 3	Immediate Action	Outcome Improvement	Sym004
First occurrence	Delay dose	Grade ≤1	Continue at same dose
		Grade 2	Reduce to 4.5 mg/kg
		No improvement	Discontinue
Second occurrence	Delay dose	Grade ≤1	Continue at same dose
		Grade 2	At dose of 6.0 mg/kg: Reduce to 4.5 mg/kg At dose of 4.5 mg/kg: Reduce to 3.0 mg
		No improvement	Discontinue
Third occurrence	Delay dose	Grade ≤1	Continue at same dose
		Grade 2	At dose of 6.0 mg/kg: Reduce to 4.5 mg/kg At dose of 4.5 mg/kg: Reduce to 3.0 mg/kg At dose of 3.0 mg/kg: Discontinue
		No improvement	Discontinue
Fourth occurrence	Discontinue	Any	Discontinue

Abbreviations (in alphabetical order): kg, kilogram; mg, milligram

Note: Dose reductions for 9 mg/kg loading NA. For dose delays, re-assess after ≤ 2 weeks. Longer delays are allowed if no recovery to < Grade 2 after 2 weeks

Table 25: Dose Reduction for Grade 3 Dermatologic AEs - Futuximab or Modotuximab

Dermatologic AE Grade 3	Immediate Action	Outcome Improvement	Futuximab or Modotuximab
First occurrence	Delay dose	Grade ≤1	Continue at same dose
		Grade 2	Reduce to 1.5 mg/kg
		No improvement	Discontinue
Second occurrence	Delay dose	Grade ≤1	Continue at same dose
		Grade 2	At dose of 3.0 mg/kg: Reduce to 1.5 mg/kg At dose of 1.5 mg/kg: Discontinue
		No improvement	Discontinue

Abbreviations (in alphabetical order): kg, kilogram; mg, milligram

Note: Dose reductions for 9 mg/kg loading NA. For dose delays, re-assess after ≤ 2 weeks. Longer delays are allowed if no recovery to < Grade 2 after 2 weeks

In each case, the next treatment should be delayed, and the patient's condition should be re-assessed after 1-2 weeks. Treatment should be delayed further if the AE remains at Grade 3 after 2 weeks.

In the case of a Grade 2 dermatologic AE which is locally debilitating for the patient, the guidelines outlined above may be followed at the Investigator's discretion.

Patients must be withdrawn from IMP treatment in the event of a Grade 4 dermatologic AE.

Appendix 8 Management of Hypomagnesemia

A. Grading of Hypomagnesemia and QTc Prolongation

Table 26: CTCAE Grading of Hypomagnesemia and QTc Prolongation

Event	1	2	3	4	5
Hypomagnesemia	<LLN-1.2 mg/dL <LLN-0.5 mmol/L	<1.2-0.9 mg/dL <0.5-0.4 mmol/L	<0.9-0.7 mg/dL <0.4-0.3 mmol/L	<0.7mg/dL <0.3 mmol/L life-threatening consequences	Death
ECG QT-corrected interval prolonged	QTc 450-480 ms	QTc 481-500 ms	QTc ≥ 501ms on at least 2 separate ECGs	QTc ≥ 501 or ≥ 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	--

Abbreviations (in alphabetical order): CTCAE, Common Terminology Criteria for Adverse Events v5; dL, deciliter; ECG, electrocardiogram; L, liter; LLN, lower limit of normal; mg, milligram; mmol, millimole; ms, millisecond; QTc, QT-corrected interval

B. Management of Hypomagnesemia

Patients receiving IMP will be monitored weekly for evidence of hypomagnesemia, which should be managed as follows (**Table 27**):

Table 27: Management of Hypomagnesemia and QTc Prolongation

Grade	Action
Grade 1-2	No replacement therapy required, weekly monitoring to continue, but may be administered at treating physician's discretion, weekly monitoring to continue
Grade 2 or higher	Use of concomitant QTc-prolonging drugs* should be discontinued unless urgently needed for medical care and no alternative therapy is available
Grade 3-4	Administer $MgSO_4$ (6 to 10g IV) at minimum 2 times per week until ≤ Grade 1 Perform predosing ECG (required) to monitor for QTc prolongation** In the event of Grade 3 QTc prolongation potentially due to hypomagnesemia, Sym004 administration should be delayed while magnesium repletion is undertaken Sym004 may be restarted with continued intensive magnesium therapy at the same dose or at a reduced dose once hypomagnesemia returns to ≤ Grade 1 severity, and once the QTc returns to WNL or baseline status In the event of Torsade de pointes (TdP) or other life-threatening arrhythmias discontinue Sym004
Grade 4	For Grade 4 hypomagnesemia that is refractory to IV magnesium-replacement therapy, dosing with IMP should be delayed or reduced.

Abbreviations (in alphabetical order): g, gram; IV, intravenous

* Listings of QTc prolonging drugs may be found at: <https://crediblemeds.org/index.php?cID=222>
** ECG is required before IMP administration to monitor QT prolongation that may result in severe arrhythmias such as TdP.

Appendix 9 Maximum Total Blood Collection Volumes

Table 28: Maximum Total Blood Collection Volumes

Study Assessments	Vol/ sample	Screen		C1		C2		C#		EOT			1M FUP	Total Volume
		#	Vol mL	#	Vol mL	#	Vol mL	#	Vol mL	#	Vol mL	#	Vol mL	
*Genomic Analysis	20+20^	*1*	40	*0*		*1*	20	*0*		*1*	20	*0*		80
Hematology Panel	5	*1*	5	*2*	10	*1*	5	*1*	5	*1*	5	*1*	5	35
Biochemistry Panel	10	*1*	10	*2*	20	*1*	10	*1*	10	*1*	10	*1*	10	70
Serum Mg, Ca, K	5	*0*		*2*	10	*3*	15	*3*	15	*0*		*0*		40
Coagulation Panel	5	*1*	5	*1*	5	*1*	5	*1*	5#	*1*	5	*1*	5	30
Pregnancy Test	5	*1*	5	*1*	5	*0*		*0*		*1*	5	*0*		15
**ADA Testing	5	*1*	5	*2*	10	*1*	5	*1*	5##	*1*	5	*1*	5	35
**PK Studies	5	*0*		*11*	55	*7*	35	*4*	20	*1*	5	*1*	5	120
**Pharmacodynamic Testing	20	*1*	20	*0*		*1*	20	*0*		*1*	20	*0*		60
Total Volume			90		115		115		60		75		30	**485**

Abbreviations (in alphabetical order): #, number of samples; 1M FUP, 1-month follow-up; ADA, anti-drug antibody; C, cycle(s); Ca, calcium; EOT, end of treatment; K, potassium; Mg, magnesium; mL, milliliter; PK, pharmacokinetic; Vol, volume

***As of Amendment 5: Omitted with the exception of prescreening genomic sampling for eligibility assessment**
****As of Amendment 5: Omitted**

^Whole blood (~ 2 × 10 mL) to be collected at each timepoint (plus additional ~ 2 × 10 mL at prescreening to be stored for assay validation purposes); for assessment of ctDNA by *Guardant360*

#C3 only
##Odd number cycles only

If sites can perform hematology, serum chemistry, and coagulation studies with smaller volumes of blood per sample, they are encouraged to do so. Required PK, ADA, and PD/biomarker volumes are fixed and should not be reduced.

To estimate a patient's total blood collection volume during study participation, maximum estimates are used. During a patient's study participation, the maximum amounts of venous blood that will be collected are listed above. Study duration is based on 12 weeks estimated average patient participation, i.e., an average of Cycle 1 (4 weeks) plus Cycle 2 and 3 (8 weeks).

When an indwelling catheter (or equivalent venous access) is utilized, a blood flush discard of up to 3 mL is to be done before drawing the first blood tube collected on the scheduled day/time for routine laboratory tests and PK samples. **Blood flush discard volumes ARE NOT included in volume calculations in table above and should be considered when summarizing actual blood collection volumes.**

Appendix 10 Schedule of Study Activities

Table 29: Schedule of Study Activities

STUDY ASSESSMENTS	Screen	CYCLE 1				CYCLE 2					SUBSEQUENT CYCLES					EOT *≤10d after decision to discontinue*	1M FUP* *30 d (+7) after last dose*	Extended Follow Up* *for ongoing AE*	As Clinically Indicated
		D1	D8 ±2	D15 ±2	D22 ±2	D1 ±2	D8 ±2	D15 ±2	D22 ±2	End of Cycle 2 *(final week or prior to C3D1 dosing)*	D1 ±2	D8 ±2	D1 5 ±2	D22 ±2	End of Even Number Cycles *(final week or prior to CxD1 dosing)*				
CONSENT AND MEDICAL HISTORY																			
Informed Consent	X																		
Eligibility Assessment	X																		
Demography	X																		
Past Medical History	X	X[a]																	
History of mCRC	X																		
SAFETY ASSESSMENTS *(screening within 14 days prior to first dose of IMP unless otherwise specified)*																			
Medication/Procedure Survey	from 14 days prior to 1st dose through 30 days after last dose																		
AE Reporting [1]	from signing of informed consent through 30 days after last dose; through 2-month (or 4-month) follow-up with continuing IMP-related (S)AEs																		X
ECOG PS Evaluation	X	X[a]				X					X					X	X		X
Vital Signs	X	SOI EOI	X	X	X	X	X	X	X		X	X	X	X		X	X		X
Physical Exam/include weight, skin [2]	X	X[a]				X					X					X	X		X
Dermatologic Exam [3]			X	X	X		X	X	X			X	X	X					X
Hematology [4]/Biochemistry Panel [5]	X	X[a]		X		X					X					X	X		X
Serum Mg, Ca, K [6]			X		X		X	X	X			X	X	X					X
Coagulation Panel [7]/Urinalysis [8]	X	X[a]				X					C3 only					X	X		X
Pregnancy Test [9] *(w/in 2d of 1st dose)*	X	X														X			X
ECG (12-lead) [10]	X	X				X					C3 only					X			X
SPECIALTY ASSESSMENTS *(on study assessments)*																			
**Blood for ADA Assessment [11] *(see Specialty Assessments Table)*		X		X		X					Odd # Cs					X	X		
**Blood for PK Assessment [12] *(see Specialty Assessments Table)*		SOI EOI 6h 24h D4	SOI EOI	SOI EOI	SOI EOI	SOI EOI			SOI EOI 6h 24h D25		SOI EOI		SOI EOI			X	X		
SPECIALTY ASSESSMENTS *(screening within 14 days prior to first dose of IMP)*																			
*Blood for Genomic Analysis [13]	Prescreen									D25 ±1d						X[c]			Upon PD if different
**Blood for Pharmacodynamics[14]	Screening/ prior to C1D1									D25 ±1d						X[c]			Upon PD if different
**Skin Bx for Pharmacodynamics[14]	Screening/ prior to C1D1					EOC1				D25 ±1d									
**Tumor Bx for Pharmacodynamics[14]	Screening/ prior to C1D1									D25 ±1d									

Table 29: Schedule of Study Activities

STUDY ASSESSMENTS	Screen	CYCLE 1				CYCLE 2					SUBSEQUENT CYCLES					EOT	1M FUP*	Extended Follow Up*	As Clinically Indicated
		D1	D8 ±2	D15 ±2	D22 ±2	D1 ±2	D8 ±2	D15 ±2	D22 ±2	End of Cycle 2 *(final week or prior to C3D1 dosing)*	D1 ±2	D8 ±2	D15 ±2	D22 ±2	End of Even Number Cycles *(final week or prior to CxD1 dosing)*	*≤10d after decision to discontinue*	*30 d (+7) after last dose*	*for ongoing AE*	
DISEASE ASSESSMENTS *(screening within 14 days prior to first dose of IMP)*																			
***Imaging for Tumor Measurements [15]	X									X					X	x[b]			
***Response Assessment [16]										X					X	x[b]			
TRIAL TREATMENT																			
IMP Infusion/Post Inf. Monitoring		X	X	X	X	X	X	X	X		X	X	X	X					

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; ADA, anti-drug antibody; AE, adverse event; Bx, biopsy; C, cycle; Ca, calcium; d/D, day; ECG, electrocardiogram; EOT, end of treatment; EOC1, End of Cycle 1; EOI, end of infusion; K, potassium; Mg, magnesium; PK, pharmacokinetic; PS, performance status; SOI, start of infusion

*** As of Amendment 5: Omitted with the exception of prescreening genomic sampling for eligibility assessment**
****As of Amendment 5: Omitted**
*****As of Amendment 5: Frequency per either institutional guidelines or Investigator discretion until confirmation of PD**

[a] Need not be assessed prior to Cycle 1 if ≤ 7 days since screening
[b] Conduct only if > 6 weeks since the previous assessment or if discontinuing study for reasons other than documented PD prior to EOC2
[c] Need not be repeated if patient is discontinuing at the EOC2

1. AE Assessments: To be assessed from signing of ICF until 30 days following last IMP dose; continue to assess for 2-months (and if necessary 4 months) following last IMP dose if related AEs persist to confirm that events have resolved, returned to baseline status, or been adequately explained. *Investigator discretion may be used with respect to the method of contact for AE assessment. Clinical events may be followed by telephone, e-mail, or in writing; an in-person visit will not be required.*
2. Physical Examination: To include measurement of height and weight at screening, and weight during physical examinations thereafter; assessment of the skin is to be performed during each physical examination.
3. Dermatologic Examination: In addition to skin assessment performed as part of the PE during visits when PE is required (to achieve weekly dermatological assessment)
4. Hematology Panel: To include CBC with differential, ANC, and platelet count. Evaluation frequency should be increased in the event of hematologic toxicity.
5. Biochemistry Panel (nonfasting): To include Na, K, Cl, bicarbonate or carbon dioxide, BUN or equivalent, creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, Ca, Mg, phosphorous, albumin, total protein, uric acid, amylase, lipase, and CK. Evaluation frequency should be increased in the event of significant serum chemistry abnormalities. Clinically significant electrolyte abnormalities should be corrected prior to dosing.
6. Serum Magnesium, Calcium, and Potassium: To include magnesium, calcium, and potassium assessments in addition to testing performed as part of the biochemistry panel during visits when biochemistry panel is required (to achieve weekly magnesium, calcium, and potassium assessment)
7. Coagulation Panel: To include PTT (or aPTT), PT/INR
8. Urinalysis: Multi-panel chemical test strip analysis acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and blood. Perform microscopic examination of sediment, if clinically indicated (may include assessment of cells [WBC and RBC per high power field] and casts).
9. Pregnancy Testing: Serum at Screening, serum or urine thereafter. Frequency may be increased as indicated, based on local requirements.
10. ECG (12-Lead): In addition to scheduled EGCs, perform in the event of documented ≥ Grade 3 hypomagnesemia and if otherwise clinically indicated.
11. ADA **(Specialty Lab)**: See in-text table for timepoints. Whole blood (~5 mL/timepoint) to be collected for serum acquisition. If a collected sample is inadequate or insufficient, analysis may be done using a PK serum sample from the same timepoint, if available. A detailed laboratory manual will be provided.

12. PK Sampling **(Specialty Lab)**: See in-text table for timepoints. Whole blood (~5 mL/timepoint) to be collected for serum acquisition. If a collected sample is inadequate or insufficient, analysis may be done using an ADA serum sample from the same timepoint, if available. A detailed laboratory will be provided. PK sampling times may be adjusted according to early trial results to optimize evaluation.
13. Genomic Analysis **(Specialty Lab)**: Peripheral blood at prescreening (~40 mL) to be collected as 4×10 mL; 2×10mL to be submitted for mutation analysis required for eligibility; remaining 2×10 mL to be stored for assay validation purposes. Thereafter, 2×10mL to be collected. Where blood sample is to be drawn on the day of biopsy (skin; tumor if performed), blood collection to occur prior to performing biopsy procedure(s). A detailed laboratory manual will be provided.
    EOC2 sample coincides with "prior to crossover" for patients in Arm B and Arm C.
    EOT sample need not be repeated in patients discontinuing at the EOC2.
    Final timepoint = EOT with Sym004.
    Additional sample to be obtained at the time of radiographic documentation of PD, if different from other required timepoints
14. Pharmacodynamic Analysis **(Specialty Lab)**: Peripheral blood collection, skin biopsies (from rash-free area), and tumor biopsies to be performed. Screening assessment may be conducted at any time after confirmation of eligibility and prior to C1D1. End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle; EOC2 sample collection preferred on Day 25 (± 24 hours) to coincide with PK sampling and genomic analysis. Where blood sample is to be drawn on the day of biopsy (skin; tumor if performed), blood collection to occur prior to performing biopsy procedure(s). A detailed laboratory manual will be provided. Additional sample to be obtained at the time of radiographic documentation of PD, if different from other required timepoints.
15. Imaging for Tumor Measurements: To include imaging by CT or MRI of the chest, abdomen and pelvis, and other sites as indicated based on tumor location and clinical judgment. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated. The same method(s) and technique should be used throughout study.
    Response Assessment: To be assessed by the Investigator or qualified designee per RECIST v1.1. Note as CR, PR, SD, PD, or NE at each evaluation point for patient management purposes and to make decisions on continued study treatment

As of Amendment 5: The visit schedule for the treatment period will apply as specified above, with indicated exceptions. Once IMP has been discontinued, an EOT visit will be performed within 7 to 10 days from the decision to withdraw treatment, and a 1M FUP visit will be performed 30 days (+7 days) following the last dose.

19 SUMMARY OF CHANGES

19.1 Protocol Amendment 1 dated 02-Jan-2018

- Previously premedication to reduce the risk of IRRs was required prior to all doses in Cycle 1, and thereafter if a patient was without evidence of IRRs the Investigator could opt to withdraw premedication on a patient-by-patient basis. With this amendment, premedication to reduce the risk of IRRs is required prior to all doses of study drug; withdrawal of premedication is not permitted at any time.
- Given the risk of hypocalcemia and hypokalemia, the monitoring plan has been amended to include more frequent serum calcium and potassium assessments in all patients. Calcium and potassium are now to be monitored weekly, at the same frequency as specified for magnesium monitoring.
- Previously the protocol stated that non-evaluable or discontinued patients would be replaced. With this amendment it is now stipulated that non-evaluable patients and patients discontinuing from study prior to the EOC2 due to either documented PR or for reasons other than documented PD, will not be replaced.
- Previously Exclusion Criterion 6f (in the synopsis only) suggested that patients with coagulation parameter abnormalities at baseline would not be eligible. This incomplete text (meant to outline PT and PTT entry criteria) was holdover from an early draft and was included in version 1 in error; it has been removed. The Sponsor feels it is not necessary to set eligibility based on PT/PTT as data collected thus far on Sym004 administration do not suggest Sym004 adversely affects these parameters.
- Although there are restrictions on prior and concomitant immunosuppressive or systemic hormonal therapy, the protocol previously allowed oral replacement glucocorticoid therapy for patients with preexisting adrenal insufficiency only. With this amendment this allowance has been broadened to allow hormone replacement therapy at standard doses for (unspecified) end-organ failure that can be adequately managed in this way.
- Pre- and post-dosing (end of Cycles 1 and 2) skin biopsies have been added for exploratory pharmacodynamic evaluation. Samples will be assessed for EGFR expression and downstream signaling, marker(s) of proliferation, and other exploratory parameters.
- Minor formatting adjustments and wording corrections have been made.

Refer to **Table 30** for the changes in Protocol Amendment 1.

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Trial Objectives: Exploratory Objectives	To evaluate potential predictive and/or prognostic biomarkers of response to treatment (peripheral blood to be collected)	To evaluate potential predictive and/or prognostic biomarkers of response to treatment (peripheral blood and skin biopsies to be collected)
1 Synopsis: Trial Design: Design Summary	Non-evaluable patients and patients discontinuing from study prior to the EOC2 for reasons other than documented PD will be replaced (every effort will be made to obtain imaging studies at the time of discontinuation).	Non-evaluable patients and patients discontinuing from study prior to the EOC2 for reasons other than documented PD will not be replaced (every effort will be made to obtain imaging studies at the time of discontinuation).
1 Synopsis: Patient Selection: Key Eligibility Criteria	**Patients to be Excluded** 6. Patients with any of the following serum chemistry abnormalities at baseline: f. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant for a prior thrombotic event, as determined by the Investigator): 12. Patients with any unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, and/or peripheral neuropathy	**Patients to be Excluded** 6. Patients with any of the following serum chemistry abnormalities at baseline: *Bullet point f. has been removed* 12. Patients with any unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, peripheral neuropathy, and/or end-organ failure being adequately managed by hormone replacement therapy
1 Synopsis: IMP Administration: Premedication	**Premedication for Infusion-Related Reactions (IRRs)** Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMPs during Cycle 1.	**Premedication for Infusion-Related Reactions (IRRs)** Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP.
1 Synopsis: Toxicity Management: Hypomagnesemia, Hypocalcemia, and Hypokalemia	*Synopsis: Toxicity Management: Hypomagnesemia* Patients will be monitored weekly for hypomagnesemia.	*Added hypocalcemia and hypokalemia to section heading* Patients will be monitored weekly for hypomagnesemia, hypocalcemia, and hypokalemia.
1 Synopsis: Study Assessments: ADA, PK, Genomic, and Pharmacodynamic Assessments	*Synopsis: Study Assessments: ADA, PK, and Genomic Assessments*	*Added pharmacodynamic to section heading* **Pharmacodynamic Analyses** (Specialty Lab) Skin biopsies for potential predictive and/or prognostic biomarker assessment
1 Synopsis: Discontinuation and Follow-Up: Replacements	Patients will be replaced if they are not evaluable (NE) for antitumor activity assessment, as defined.	After randomization to the study, no patients will be replaced. Patients not evaluable (NE) for antitumor activity assessment, as defined, or patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD, will not be replaced.

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Analysis Plan: Statistical Methods	**Safety Analyses** Special attention will be paid to dermatologic toxicities, hypomagnesemia, and infusion reactions.	**Safety Analyses** Special attention will be paid to dermatologic toxicities, hypomagnesemia, hypocalcemia, hypokalemia, and infusion reactions.
3.1.3 Exploratory Objective	To evaluate potential predictive and/or prognostic biomarkers of response to treatment (peripheral blood to be collected)	To evaluate potential predictive and/or prognostic biomarkers of response to treatment (peripheral blood and skin biopsies to be collected)
3.2 Trial Design Summary	Dosing Schedule Beginning with the first dose, all patients will be premedicated with standard therapies for at minimum prior to each Cycle 1 dose to reduce the risk of infusion-related reactions (IRRs), and must be premedicated with standard therapies throughout at minimum Cycles 1 and 2 to reduce the risk of anti-EGFR-related dermatological adverse events (AEs). Thereafter, premedication of individuals for both potential toxicities is at the Investigator's discretion and as needed.	Dosing Schedule Beginning with the first dose, all patients will be premedicated with standard therapies prior to each dose to reduce the risk of infusion-related reactions (IRRs), and must be premedicated with standard therapies throughout at minimum Cycles 1 and 2 to reduce the risk of anti-EGFR-related dermatological adverse events (AEs).
	Criteria for Evaluability Non-evaluable patients and patients discontinuing from study prior to the EOC2 for reasons other than documented PD will be replaced (every effort will be made to obtain imaging studies at the time of discontinuation).	Criteria for Evaluability Non-evaluable patients and patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD will not be replaced (every effort will be made to obtain imaging studies at the time of discontinuation).
	Not applicable	Safety Monitoring A Study Safety Committee will be established and will be comprised of participating Investigator(s) and the Sponsor's Medical Representative(s). Study Safety Committee Teleconferences will be held at intervals to discuss ongoing patient status and any emerging safety concerns; frequency of teleconferences may fluctuate based on accrual and study activity, as indicated.

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	Study Assessments For safety, patients will be monitored throughout the treatment and 1-month follow-up (1M FUP) period for changes in: clinical status, physical exam findings (including weekly assessments for dermatologic AEs); laboratory data (including weekly assessments for hypomagnesemia); and electrocardiogram (ECG) findings… Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing including at the time of documented progression or study discontinuation for other reasons.	Study Assessments For safety, patients will be monitored throughout the treatment and 1-month follow-up (1M FUP) period for changes in: clinical status, physical exam findings (including weekly assessments for dermatologic AEs); laboratory data (including weekly assessments for hypomagnesemia, hypocalcemia, and hypokalemia); and electrocardiogram (ECG) findings… Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing including at the time of documented progression or study discontinuation for other reasons, and in skin biopsies obtained prior to and following Cycle 1 and Cycle 2 dosing.
4.1.2 Planned Sample Size	Note: …Non-evaluable patients and patients discontinuing from study prior to the EOC2 for reasons other than documented PD will be replaced.	Note: …Non-evaluable patients and patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD, will not be replaced.
4.2 Criteria for Inclusion	*Note for inclusion criterion 10:* A highly effective method of contraception is defined as non-hormonal contraception equivalent to a double-barrier method (e.g. double-barrier method or single-barrier method in combination with a spermicide or intrauterine device). Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within ≤ 2 working days prior to administration of the first dose of IMP.	*Note for inclusion criterion 10:* A highly effective method of contraception is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide or intrauterine device). Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within ≤ 2 working days prior to administration of the first dose of IMP.
4.3.1 Patients to be Excluded	12. Patients with other unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, and/or peripheral neuropathy	12. Patients with any unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy with the exception of persistent Grade 2 alopecia, decreased hemoglobin, peripheral neuropathy, and/or end-organ failure being adequately managed by hormone replacement therapy
4.3.2 Drugs and Other Treatments to be Excluded	5. Immunosuppressive or systemic hormonal therapy…The following therapies are allowed: c. Oral replacement glucocorticoid therapy for adrenal insufficiency	5. Immunosuppressive or systemic hormonal therapy…The following therapies are allowed: c. Hormone replacement therapy at standard doses for end-organ failure

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.5.4.7 Premedication for Infusion-Related Reactions	There is an inherent risk for IRRs with the administration of mAbs, therefore premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP during Cycle 1. If a patient is without evidence of IRRs after Cycle 1, the Investigator may choose, on a patient-by-patient basis, to withdraw premedication with subsequent dosing to determine whether such continued therapy is necessary in that patient. All patients will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen. Recommended premedication doses are provided. Should a patient experience an IRR while on study, including after Cycle 1, guidelines for premedication following an IRR are provided. Guidelines for the grading and management of IRRs of all severities are also provided.	There is an inherent risk for IRRs with the administration of mAbs, therefore premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP. All patients will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen. Recommended premedication doses are provided. Should a patient experience an IRR while on study, guidelines for premedication following an IRR are provided. Guidelines for the grading and management of IRRs of all severities are also provided.
6.9 Concurrent Treatments and Supportive Care	1. Prophylaxis for IRRs, Dermatologic AEs, and Other IMP-Related AEs (Sym004): Premedications for IRRs and dermatologic AEs are mandatory during Cycle 1 and during Cycles 1 and 2, respectively, and as indicated thereafter based on the occurrence of related AEs…	1. Prophylaxis for IRRs, Dermatologic AEs, and Other IMP-Related AEs (Sym004): Premedications for IRRs are mandatory throughout the study. Premedications for dermatologic AEs are mandatory during Cycles 1 and 2, and as indicated thereafter based on the occurrence of related AEs…
7.2.7.3 Serum Magnesium, Calcium, and Potassium	*7.2.7.3 Serum Magnesium* (Timepoints shown are in addition to testing performed as part of scheduled biochemistry panels; intention is to achieve weekly magnesium testing during the treatment period)	*Added calcium and potassium to section heading* (Timepoints shown are in addition to testing performed as part of scheduled biochemistry panels; intention is to achieve weekly magnesium, calcium, and potassium testing during the treatment period)
7.3 Specialty Assessments	*7.3 Immunogenicity and Pharmacokinetic Assessments (Specialty Laboratory)* …Blood samples will be taken according to the schedule shown. Every effort will be made to collect ADA and PK samples at the timepoints specified…	*Section heading renamed to Specialty Assessments* …Blood samples and skin biopsies will be taken according to the schedule shown. Every effort will be made to collect samples at the timepoints specified…
7.3.2 Exploratory Pharmacokinetic Assessment (Specialty Laboratory)	(…Data will also enable population PK modeling for further PK characterization)	(…Data will also enable population PK modeling for further PK characterization; serum to be isolated) *Removed "*Disease/Tumor Assessments*" text included in the Note at the end of the section.*

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.3.3 Genomic Analysis in Peripheral Blood (Specialty Laboratory)	• Cycle 2 o Day 25 (± 24 hours) (coincides with PK sampling for all patients and "prior to crossover" for patients in Arm B and C)	• Cycle 2 o Day 25 (± 24 hours) (coincides with PK sampling and skin biopsy for all patients and "prior to crossover" for patients in Arm B and C)
7.3.4 Pharmacodynamic Analysis in Skin Biopsies (Specialty Laboratory)	*Not applicable as this is a new section*	(To be performed after eligibility has been confirmed. Biopsy specimens will be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. Skin biopsies are requested from a rash-free area) (Samples will be assessed for EGFR expression and downstream signaling, markers(s) of proliferation, and other exploratory parameters) • Screening (after confirmation of eligibility)* • EOC1** • EOC2** o Day 25 (± 24 hours) (coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arm B and C) *Screening assessments may be conducted at any time prior to C1D1, including on C1D1 prior to dosing. ***End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing. The purpose of pharmacodynamic assessments is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Sym004, and that may change with the possible development of acquired resistance.
8.1.1.2 Premedication for IRRs (Beginning at Cycle 1)	Premedication for prophylaxis of IRRs will be mandatory prior to each dose of Sym004 during Cycle 1. The following agents are required during Cycle 1; recommended doses are provided… If a patient is without evidence of IRRs after Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion.	Premedication for prophylaxis of IRRs will be mandatory prior to each dose of Sym004. The following agents are required; recommended doses are provided… *This text has been removed*

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
8.1.1.3 Premedication for IRRs (Following an IRR)	• For Grade 1 or Grade 2 reactions, premedication prior to subsequent infusions should be considered. Thereafter, if a patient is without recurrence of an IRR, the Investigator may choose to withdraw premedication to determine whether such continued therapy is necessary for that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion (e.g. by reduction in dose, frequency, or number of agents administered, at the Investigator's discretion). For those patients who experience recurrent signs/symptoms suggestive of an IRR, premedication should be re-instituted for at minimum 2 additional doses before any future attempt to withdraw. • For Grade 3 reactions, premedication prior to subsequent infusions will be required (if the patient is to be retreated).	• For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedications for subsequent infusions.
9.2 Replacements	Patients will be replaced if they are NE for antitumor activity assessment, as defined.	After randomization to the study, no patients will be replaced. Patients NE for antitumor activity assessment, as defined, or patients discontinuing from study prior to the EOC2 due to either documented PD or for reasons other than documented PD, will not be replaced.
11.1 Precautions Regarding Procreation	"A highly effective method of contraception" is defined as non-hormonal contraception equivalent to a double-barrier method (e.g. double-barrier method can be single-barrier method in combination with a spermicide or intrauterine device).	"A highly effective method of contraception" is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide or intrauterine device).
11.2 Infusion-Related Reactions	Premedication to reduce the risk of IRRs associated with IMP administration is required during Cycle 1 and following the occurrence of an IRR.	Premedication to reduce the risk of IRRs associated with IMP administration is required.
11.4 Hypomagnesemia, Hypocalcemia, and Hypokalemia	*11.4 Hypomagnesemia* Patients receiving IMP will be monitored weekly for evidence of hypomagnesemia.	*Added hypocalcemia and hypokalemia to section heading* Patients receiving IMP will be monitored weekly for evidence of hypomagnesemia, hypocalcemia, and hypokalemia.
14.4 Publications	Authorship will be determined by agreement.	Authorship will be determined by agreement with the Coordinating Investigator and Study Steering Committee.
16.7.1 Safety Analysis	Special attention will be paid to dermatologic toxicities, hypomagnesemia, and infusion reactions.	Special attention will be paid to dermatologic toxicities, hypomagnesemia, hypocalcemia, hypokalemia, and infusion reactions.
16.7.3 Exploratory Biomarker Analysis	Biomarker assessments, to include collection of peripheral blood, will be conducted in all patients and will evaluate potential predictive and/or prognostic biomarkers of response to treatment…	Biomarker assessments, to include collection of peripheral blood and skin biopsies, will be conducted in all patients and will evaluate potential predictive and/or prognostic biomarkers of response to treatment…

Table 30: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
18 Appendices: Appendix 6: Management of Infusion-Related Reactions	Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP during Cycle 1. If a patient is without evidence of IRRs after Cycle 1, the Investigator may opt to withdraw premedication on a patient-by-patient basis with subsequent dosing in order to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion. For IRRs while on study, the following premedication instructions are provided: • For Grade 1 or Grade 2 reactions, premedication prior to subsequent infusions should be considered. Thereafter, if a patient is without recurrence of an IRR, the Investigator may choose to withdraw premedication to determine whether such continued therapy is necessary for that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion (e.g. by reduction in dose, frequency, or number of agents administered, at the Investigator's discretion). For those patients who experience recurrent symptoms suggestive of an IRR, premedication should be re-instituted for at minimum 2 additional doses before any future attempt to withdraw. • For Grade 3 reactions, premedication prior to subsequent infusions will be required (if the patient is to be retreated).	Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP. For IRRs while on study, the following premedication instructions are provided: • For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedications for subsequent infusions.

19.2 Protocol Amendment 2 dated 08-Mar-2018

- Additional peripheral blood sampling has been added for assessment of serum proteins and other potential biomarkers; timepoints and instructions are provided.
- Optional tumor biopsies have been added. Tumor biopsies, if consent is obtained, will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models. Timepoints and instructions are provided.
- Previously it was stated that patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed those regimens. With this amendment it has been clarified that patients intolerant of previous regimens may also be included.
- For study eligibility, patients must have "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC. Previously it was stated that prior therapy must have been received no more than 6 calendar months prior to randomization for this study. With this amendment the window has been changed to no more than 6

calendar months prior to consent for this trial, and it has been included that this is regardless of the line of therapy in which prior anti-EGFR therapy was used.

- Based on preclinical pharmacokinetic data, the required duration for post-dosing contraception has been changed to 3 months.
- Patients with a significant gastrointestinal abnormality, including diarrhea > Grade 1 at the time of randomization, are to be excluded. With this amendment, it is noted that an exception would be made in the case of patients with recent Grade 2 diarrhea secondary to administration of oral contrast. Such patients will be allowed, provided symptoms have resolved prior to first study drug administration.
- Coagulation studies, urinalysis, and ECG have been added as assessments to be conducted on Cycle 3 Day 1.
- The number of investigational sites planned to participate in this trial has been decreased from 30 to 20, and the number of patients per arm has been corrected from 20 to 18.
- Patients who received adjuvant chemotherapy and had documented recurrence (by imaging studies) during or within 6 months of completion of the adjuvant chemotherapy are permitted to count the adjuvant therapy as one regimen of required prior chemotherapy. With this amendment, it has been clarified that the imposed 6-month window refers to 6 calendar months.
- The inclusion criteria mutation requirements are reworded and restated as an exclusion criterion.
- The IMPs, futuximab and modotuximab, are also referred to as drug products.
- The frequency of pregnancy testing may be increased during the study, as clinically indicated, based on local requirements.
- The outcome of AEs must be assessed by the Investigator; the option of "ongoing" has been added.
- Clarified that initial SAEs and follow-up SAE information are to be submitted to the Sponsor (or designee) within 24 hours of awareness.
- Clarified that the bioanalytical assays used for Sym004 assessment will also be applied for measurement of serum concentrations of futuximab and modotuximab in the patients dosed with futuximab drug product and modotuximab drug product, respectively.
- Newly included pharmacodynamic analyses are now mentioned as an exploratory endpoint.
- Tables have been updated based on changes described.
- Formatting adjustments, outline modifications, cross-reference links and link corrections, and other minor typographical corrections and slight wording changes are included.

Refer to **Table 31** for the changes in Protocol Amendment 2.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Investigational Medicinal Products	The Investigational Medicinal Products (IMPs) in this trial are Sym004, futuximab, modotuximab. **Supplies** Sym004: Single-use clear glass vials contain: • A nominal fill volume of 20 mL • At a concentration of 25 mg/mL for a total vial content of 500 mg Futuximab and modotuximab, each: Single-use clear glass vials contain: • A nominal fill volume of 10 mL • At a concentration 25 mg/mL for a total vial content of 250 mg	The Investigational Medicinal Products (IMPs) in this trial are Sym004 (a mixture of futuximab and modotuximab), the drug product futuximab, and the drug product modotuximab. **Supplies** Sym004: Single-use clear glass vials contain: • A nominal fill volume of 20 mL • At a concentration of 25 mg/mL for a total vial content of 500 mg Futuximab: Single-use clear glass vials contain: • A nominal fill volume of 10 mL • At a concentration of 25 mg/mL for a total vial content of 250 mg Modotuximab: Single-use clear glass vials contain: • A nominal fill volume of 10 mL • At a concentration of 25 mg/mL for a total vial content of 250 mg
1 Synopsis: Trial Objectives: Secondary Objective 3.1.2 Secondary Objective	To evaluate the safety profile of a weekly dosing regimen of Sym004 versus futuximab or modotuximab.	To evaluate the safety profile of a weekly dosing regimen of Sym004 versus single agent futuximab or single agent modotuximab.
1 Synopsis: Trial Objectives: Exploratory Objective 3.1.3 Exploratory Objective	To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood and skin biopsies to be collected)*	To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood, skin biopsies, and tumor biopsies [tumor biopsies optional] to be collected). Tumor biopsies, if consent is obtained, will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models.*
1 Synopsis: Trial Design: Design Summary 12.3 Study Safety Committee	A Study Safety Committee comprised of the participating Investigators and the Sponsor's Medical Monitor(s) will review clinical and laboratory safety data on an ongoing basis throughout the trial.	Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigator(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Patient Selection: Investigational Sites 4.1.1 Investigational Sites	Number of Sites: Approximately 30 sites may participate based on anticipated accrual Expected Countries: 5-10 countries in North America and Europe	Number of Sites: Approximately 20 sites may participate based on anticipated accrual Number of Countries: Approximately 4-6 countries in North America and Europe
1 Synopsis: Patient Selection: Key Eligibility Criteria	**Patients to be Included** 7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed those regimens. 8. Patients with "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC must have: c. No more than 6 calendar months from last dose of previous anti-EGFR mAb treatment to randomization for this trial **Patients to be Excluded** 1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 6 months after the last dose of IMP. 2. Patients with a prior history of *RAS* (*KRAS* or *NRAS*), *BRAF*, or *EGFR*-ECD mutation in their tumor at the time of any previous assessment	**Patients to be Included** 7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed (includes intolerance to) those regimens. 8. Patients with "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC must have: c. No more than 6 calendar months from last dose of previous anti-EGFR mAb treatment to date of consent for this trial (regardless of the line of therapy in which it was used) **Patients to be Excluded** 1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 3 months after the last dose of IMP. 2. Patients with a prior history of any of the following mutations in their tumor at the time of any previous assessment: a. *RAS* (*KRAS* and *NRAS*) mutations in the following codons: o Exon 2: codon 12, 13 o Exon 3: codon 59, 61 o Exon 4: codon 117, 146 b. *BRAF* V600E mutation c. *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations
1 Synopsis: IMP Administration: Doses to be Administered 6.5.4.1 Dose 6.7.3 Treatment after Cycle 2	Upon crossover, Sym004 will be administered at the dose level that contains the corresponding concentration of futuximab or modotuximab as was previously being administered.	Upon crossover, Sym004 will be administered at the dose level that contains the corresponding dose level of the individual antibody futuximab or modotuximab as was previously being administered (prior to crossover).

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Safety Monitoring: Safety Monitoring	A Study Safety Committee will be established and will be comprised of the Investigators(s) and the Sponsor's Medical Representative(s). Study Safety Committee teleconferences will be held at intervals to discuss ongoing patient status and any emerging safety concerns; the frequency of teleconferences may fluctuate based on accrual and study activity, as indicated.	Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigators(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns.
1 Synopsis: Safety Assessments: ADA, PK, Genomic, and Pharmacodynamic Assessments	**Pharmacodynamic Analyses** (Specialty Lab) Skin biopsies for potential predictive and/or prognostic biomarker assessment	**Pharmacodynamic Analyses** (Specialty Lab) Peripheral blood, skin biopsies, and tumor biopsies (*tumor biopsies optional*) for potential predictive and/or prognostic biomarker assessment
2.3 Summary of Nonclinical Studies	Futuximab-, modotuximab-, and Sym004-mediated secondary effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were investigated using 51-chromium release assays in human cancer cell lines.	Futuximab-, modotuximab-, and Sym004-mediated secondary effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were investigated in human cancer cell lines.
2.4 Clinical Experience	This is the first clinical study in which the individual antibodies, futuximab and modotuximab are being administered to patients as single agents. These two antibodies have been administered as a combination in all studies of Sym004.	This is the first clinical study in which the individual antibodies, futuximab and modotuximab, are being administered to patients as single agents. These two antibodies have been administered as a combination in all human studies of Sym004 thus far.
2.4.4 Antitumor Effects	An exploratory analysis revealed that the responders to Sym004 were shown to have tumors with WT *KRAS*, *NRAS*, and *BRAF* genotype, as well as having no evidence of *MET* amplification. The antitumor results of the completed Phase 2b trial, Sym004-05, are described in Section 2.1.3.2.	From the Phase 2b trial (Sym004-05), an exploratory analysis revealed that the responders to Sym004 had tumors with WT *KRAS*, *NRAS*, and *BRAF* genotype, as well as having no evidence of *MET* amplification. The antitumor results of this trial are described in Section 2.1.3.2.
2.7 Summary of Overall Benefit and Risk	One or both antibodies may demonstrate a clinical activity similar to that of Sym004 when administered alone.	One or both antibodies administered alone may demonstrate a clinical activity similar to that of Sym004.
3.2 Trial Design Summary	<u>Patient Population</u> This is a Phase 2, open-label, 3-arm trial with randomization in the ratio of 1:1:1 to either Sym004 (Arm A), futuximab (Arm B), or modotuximab (Arm C)... Following consent and prior to randomization, centralized genomic analysis of *RAS* (*KRAS*/*NRAS*), *BRAF* V600, and *EGFR*-ECD mutation status as assessed in ctDNA will be conducted on peripheral blood samples obtained from each potential patient.	<u>Patient Population</u> This is a Phase 2, open-label, three-arm trial with randomization in the ratio of 1:1:1 to either Sym004 (Arm A), futuximab drug product (Arm B), or modotuximab drug product (Arm C)... Following consent and prior to randomization, centralized genomic analysis of *RAS* (*KRAS*/*NRAS*), *BRAF* V600, and *EGFR*-ECD mutations in ctDNA from peripheral blood samples obtained from each potential patient will be conducted.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	Safety Monitoring A Study Safety Committee will be established and will be comprised of the Investigators(s) and the Sponsor's Medical Representative(s). Study Safety Committee teleconferences will be held at intervals to discuss ongoing patient status and any emerging safety concerns; the frequency of teleconferences may fluctuate based on accrual and study activity, as indicated. Study Assessments Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing including at the time of documented progression or study discontinuation for other reasons, and in skin biopsies obtained prior to and following Cycle 1 and Cycle 2 dosing.	Safety Monitoring Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the trial. A Study Safety Committee will be established and will be comprised of participating Investigators(s) and the Sponsor's Medical Representative(s). If indicated, Study Safety Committee teleconferences will be held to discuss ongoing patient status and any emerging safety concerns. Study Assessments Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing including at the time of documented progression or study discontinuation for other reasons, in skin biopsies obtained prior to and following Cycle 1 and Cycle 2 dosing, and in tumor biopsies (*tumor biopsies optional*) obtained prior to and following Cycle 2 dosing.
4.2 Criteria for Inclusion	7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed those regimens. 8. Patients with "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC. Patients must have: c. No more than 6 calendar months from last dose of previous anti-EGFR mAb treatment to randomization for this trial 10. Patients, male and female, who are either not of childbearing potential or who agree to use a highly effective method of contraception during the study beginning within 2 weeks prior to the first dose and continuing until 6 months after the last dose of IMP.	7. Patients must have received at least 2 prior regimens of standard chemotherapy for mCRC and must have been refractory to or failed (includes intolerance to) those regimens. 8. Patients with "acquired" resistance to commercially available anti-EGFR mAbs approved for the treatment of mCRC. Patients must have: c. No more than 6 calendar months from last dose of previous anti-EGFR mAb treatment to date of consent for this trial (regardless of the line of therapy in which it was used) 10. Patients, male and female, who are either not of childbearing potential or who agree to use a highly effective method of contraception during the study beginning within 2 weeks prior to the first dose and continuing until 3 months after the last dose of IMP.
4.3.1 Patients to be Excluded	1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 6 months after the last dose of IMP. WOCBP, and fertile men with WOCBP-partner(s) not using and not willing to use a highly effective method of contraception. 2. Patients with a prior history of *RAS* (*KRAS* or *NRAS*), *BRAF*, or *EGFR*-ECD mutation in their tumor at the time of any previous assessment	1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 3 months after the last dose of IMP. WOCBP, and fertile men with WOCBP-partner(s) not using and not willing to use a highly effective method of contraception. 2. Patients with a prior history any of the following mutations in their tumor at the time of any previous assessment: a. *RAS* (*KRAS* and *NRAS*) mutations in the following codons: • Exon 2: codon 12, 13

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		• Exon 3: codon 59, 61 • Exon 4: codon 117, 146 b. *BRAF* V600E mutation c. *EGFR*-ECD V441D, V441G, S464L, G465E, G465R, S492R mutations 10. Patients with a significant gastrointestinal abnormality… Note: Patients with recent Grade 2 diarrhea secondary to administration of oral contrast are allowed, provided symptoms have resolved prior to first study drug administration.
5.1 Investigational Medicinal Products	The Investigational Medicinal Products (IMPs) are Sym004, futuximab, and modotuximab.	The Investigational Medicinal Products (IMPs) are Sym004, futuximab drug product, and modotuximab drug product.
5.1.1 Formulations	• Sym004 o Nominal fill volume of 20 mL o At a concentration of 25 mg/mL for a total vial content of 500 mg • futuximab and modotuximab (each) o Nominal fill volume of 10 mL o At a concentration 25 mg/mL for a total vial content of 250 mg	• Sym004 o Nominal fill volume of 20 mL o At a concentration of 25 mg/mL for a total vial content of 500 mg • Futuximab o Nominal fill volume of 10 mL o At a concentration of 25 mg/mL for a total vial content of 250 mg • Modotuximab o Nominal fill volume of 10 mL o At a concentration of 25 mg/mL for a total vial content of 250 mg
5.1.7 Administration of IMPs	• futuximab and modotuximab (each) (4.5/3 mg/kg) o 4.5 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min) o 3 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min)	• Futuximab (4.5/3 mg/kg) o 4.5 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min) o 3 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min) • Modotuximab (4.5/3 mg/kg) o 4.5 mg/kg loading dose on C1D1 administered in a total volume of 500 mL over 1 hour (+ 10 min) o 3 mg/kg weekly maintenance doses beginning on C1D8 administered in a total volume of 250 mL over 30 minutes (+ 10 min)
6.2.1 Recruitment Period	It is anticipated that enrollment to this study will be completed in approximately 9 months. • Anticipated date of randomization of first patient: Q4 2020 • Anticipated date of randomization of last patient: Q2 2021	It is anticipated that enrollment to this study will be completed in approximately 6 months. • Anticipated date of randomization of first patient: Q3 2018 • Anticipated date of randomization of last patient: Q4 2018

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.2.2 Trial Duration	Data Cut-off for Primary Analysis: When the required number of evaluable patients (20 patients per arm) have been treated…	Data Cut-off for Primary Analysis: When the required number of evaluable patients (18 patients per arm) have been treated…
6.3.5 Randomization	Randomization will be in blocks of 9 patients.	*Text removed*
6.9 Concurrent Treatments and Supportive Care	1. Prophylaxis for IRRs, Dermatologic AEs, and Other IMP-Related AEs (Sym004): Premedications for IRRs are mandatory throughout the study…	1. Prophylaxis for IRRs, Dermatologic AEs, and Other IMP-Related AEs: Premedications for IRRs are mandatory throughout the study…
7.2.7.4 Coagulation Panel 7.2.7.5 Urinalysis	• Cycle 2 only o Day 1 (prior to dosing)	• Cycle 2 and 3 o Day 1 (prior to dosing)
7.2.7.6 Pregnancy Testing	As clinically indicated	As clinically indicated (frequency may be increased based on local requirements)
7.2.8 Electrocardiogram	• Cycle 2 o Day 1 (prior to dosing)	• Cycle 2 and 3 o Day 1 (prior to dosing)
7.3 Specialty Assessments	Blood samples and skin biopsies will be taken according to the schedule shown.	Blood samples, skin biopsies, and tumor biopsies (*tumor biopsies optional*) will be taken according to the schedule shown.
7.3.3 Genomic Analysis in Peripheral Blood (Specialty Laboratory)	• Prescreening (for eligibility) • Cycle 2 o Day 25 (± 24 hours) (coincides with PK sampling and skin biopsy for all patients and "prior to crossover" for patients in Arm B and C) • EOT with Sym004 (need not be repeated if patient is discontinuing at the EOC2) • At the time of radiographically confirmed PD if different for the above Note: Whole blood (~ 2 × 10 mL) to be collected at each timepoint (plus additional ~ 2 × 10 mL at prescreening to be stored for assay validation purposes); for assessment of ctDNA by *Guardant360*.	• Prescreening (for eligibility) • EOC2 o Day 25 (± 24 hours) (coincides with PK sampling and pharmacodynamic sampling for all patients and "prior to crossover" for patients in Arms B and C) • EOT with Sym004 (need not be repeated if patient is discontinuing at the EOC2) • At the time of radiographically confirmed PD if different for the above Note: Whole blood (~ 2 × 10 mL) to be collected at each timepoint (plus additional ~ 2 × 10 mL at prescreening to be stored for assay validation purposes); for assessment of ctDNA by *Guardant360*; where blood sample is to be drawn on the day of biopsy (skin; tumor if performed), blood collection to occur prior to performing biopsy procedure(s).
7.3.4 Pharmacodynamic Analyses (Specialty Laboratory)	*Not applicable as this is a new section.*	7.3.4 Pharmacodynamic Analyses (Specialty Laboratory) *(To be performed after eligibility has been confirmed)* The purpose of pharmacodynamic assessments is to develop an approach for the identification and validation of biomarkers that may predict which

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		patients are likely to respond to Sym004, and that may change with the possible development of acquired resistance…
7.3.4.1 Peripheral Blood	*Not applicable as this is a new section.*	7.3.4.1 Peripheral Blood *(Samples will be assessed for serum proteins and other potential biomarkers)…*
7.3.4.2 Skin Biopsies	7.3.4 Pharmacodynamic Analysis in Skin Biopsies (Specialty Laboratory) *(To be performed after eligibility has been confirmed. Biopsy specimens will be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. Skin biopsies are requested from a rash-free area)* *(Samples will be assessed for EGFR expression and downstream signaling, markers(s) of proliferation, and other exploratory parameters)* • Screening (after confirmation of eligibility)* • EOC1** • EOC2** o Day 25 (± 24 hours) *(coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arm B and C)* **Screening assessments may be conducted at any time prior to C1D1, including on C1D1 prior to dosing.* ****End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.* The purpose of pharmacodynamic assessments is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Sym004, and that may change with the possible development of acquired resistance.	7.3.4.2 Skin Biopsies *(Biopsy specimens to be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory techniques. Skin biopsies are requested from a rash-free area)* *(Samples will be assessed for various parameters, which may include but are not limited to EGFR expression and downstream signaling, markers(s) of proliferation, genomic alterations, etc.)* • Screening (after confirmation of eligibility)* • EOC1** • EOC2** o Day 25 (± 24 hours) *(preferred day of sampling; coincides with PK sampling and genomic analysis for all patients and "prior to crossover" for patients in Arms B and C)* **Screening sampling may be conducted at any time prior to C1D1, including on C1D1 prior to dosing.* ***End of Cycle sampling may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.* Note: Procedure to be performed after collecting blood sample for pharmacodynamic analyses.
7.3.4.3 Tumor Biopsies (Optional)	*Not applicable as this is a new section.*	7.3.4.3 Tumor Biopsies *(Optional)* *(Samples will be assessed for various parameters, which may include but are not limited to EGFR expression and downstream signaling, markers(s) of proliferation, genomic alterations, etc.)…*
8.1.1.2 Premedication for IRRs	8.1.1.2 Premedication for IRRs (Beginning at Cycle 1) Premedication for prophylaxis of IRRs will be mandatory prior to each dose of Sym004.	8.1.1.2 Premedication for IRRs Premedication for prophylaxis of IRRs will be mandatory prior to each dose of IMP.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
9.1 Criteria for Treatment Discontinuation	1. Progressive Disease:… *(patients receiving futuximab or modotuximab may opt to crossover and receive Sym004)* 2. Clinical Progression:… *(patients receiving futuximab or modotuximab may opt to crossover and receive Sym004)*	1. Progressive Disease:… *Note: Patients receiving futuximab or modotuximab with documented PD at the EOC2 (or prior to the EOC2) will be offered the opportunity to crossover to receive Sym004 or will be discontinued from study.* 2. Clinical Progression:… *Removed italicized text*
10.1.2 Events Not to be Considered as Adverse Events	*PD may be reported as an AE/SAE in the case of patient death, with death being the outcome of the event, but only when the nature of the PD is different than expected.*	Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.
10.1.5 Events That Do Not Meet the Definition of Serious Adverse Events	*PD may be reported as an SAE in the case of patient death, with death being the outcome of the event, but only when the nature of the PD is different than expected.*	Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.
10.2.1 Information to be Provided for Each AE	• **Outcome** The outcome of the AE must be assessed by the Investigator utilizing one of the following options: o Recovered/resolved o Recovered/resolved with sequelae o Recovering/resolving o Not recovered/not resolved o Fatal o Unknown	• **Outcome** The outcome of the AE must be assessed by the Investigator utilizing one of the following options: o Recovered/resolved o Recovered/resolved with sequelae o Recovering/resolving o Not recovered/not resolved o Ongoing o Fatal o Unknown
10.3.1 Timeframes for Reporting to the Sponsor	In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. Timelines for reporting of SAEs and SAE follow-up information are shown (Table 8).	In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness. *Removed Table 8: Timelines for Submission of SAEs and SAE Follow-up*
10.4 Pregnancy	Elective terminations for non-medical reasons should not be reported as AEs.	Elective terminations for non-medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
11.1 Precautions Regarding Procreation	Studies have not been performed to determine whether Sym004, futuximab, or modotuximab affect reproductive function in males. For this reason, men with partners with childbearing potential must use a highly effective method of contraception while receiving IMP. Women and men of childbearing potential… must use highly effective contraception within 2 weeks prior to the first dose and continuing until 6 months after final administration of IMP.	Studies have not been performed to determine whether Sym004, futuximab, or modotuximab affect reproductive function in males or can cause fetal harm. For this reason, men with partners of childbearing potential must use a highly effective method of contraception while receiving IMP. Women and men of childbearing potential… must use highly effective contraception within 2 weeks prior to the first dose and continuing until 3 months after final administration of IMP.
13.4.1. Modification of the Study Protocol	If modifications in the experimental design… and approval by the appropriate review committees, except where necessary to immediately eliminate apparent hazards to patients.	If modifications in the experimental design… and approval by the appropriate regulatory authority (as indicated) and review committees, except where necessary to immediately eliminate apparent hazards to patients.
13.4.2 Modification of the Informed Consent Form	If modifications to the experimental design, dosages, assessments, patient selection, etc. of the protocol are indicated or required, and if such modifications substantially alter the study design or increase the potential risk to patients, the Investigator will prepare a revision to the existing ICF. Such a revision will be reviewed and approved by the appropriate IRB/EC, and documentation of this approval will be forwarded to the Sponsor (or designee) for submission to the appropriate regulatory body.	If modifications to the experimental design, dosages, assessments, patient selection, etc. of the protocol are indicated or required, and if such modifications substantially alter the study design or increase the potential risk to patients, the Sponsor (or designee) will prepare a revision to the existing sample ICF for modification, as appropriate, by each Investigator. Any revision to the sample ICF prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) SOPs. Such a revision will be reviewed and approved by the appropriate regulatory authority (as indicated) and IRB/EC.
14.1 Medical Supervision	An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Part 312 and ICH E6(R2) GCP.	An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Parts 50, 56, and 312 and/or by governing Health Authorities, as well as ICH E6(R2) GCP.
14.11 Record Retention	Regulatory authorities require that the Investigator retain copies of all files pertaining to the study (i.e. records of IMP disposition, signed ICFs, CRFs, all correspondence, dates of monitoring visits, and records which support them) for a period of 2 years following the date of marketing application approval of the drug, for the indication that is the subject of the study. If no application is filed, or the application is not approved for the indication under study, all files pertaining to the study are to be maintained for 2 years after the investigation is discontinued and governing Health Authorities have been so notified.	Regulatory authorities require that the Investigator retain copies of all files pertaining to the study according to local requirements.

Table 31: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
15.3 Data Processing	*Not applicable*	Once recorded within the electronic CRF, study data will pass through a set of pre-programmed data validation checks designed to identify inconsistencies and other data errors, and will undergo an additional study-specific data review process, as stated above in Section 15.2. Data issues will be queried via the EDC system and query resolutions will be documented.
16.4.2.1 Pharmacokinetic (PK) Endpoints	The PK profile of the study drugs will be derived based on the concentration time curves after the first and the 8th infusion on Cycle 2, Day 22. For patients dosed with Sym004, the serum concentration of futuximab and modotuximab will be measured in separate bioanalytical assays. The sum of futuximab and modotuximab is defined as the Sym004 serum concentration.	The PK profile of the IMPs will be derived based on the concentration time curves after the first and the 8th infusion on Cycle 2, Day 22. For patients dosed with Sym004, the serum concentration of futuximab and modotuximab will be measured in separate bioanalytical assays. The Sym004 serum concentration is defined as the sum of futuximab and modotuximab serum concentrations measured in a sample. The bioanalytical assays used for Sym004 assessment will also be applied for measurement of serum concentrations of futuximab and modotuximab in the patients dosed with futuximab drug product and modotuximab drug product, respectively.
16.8 Exploratory Analysis 16.8.1 Exploratory Biomarker and Pharmacodynamic Analyses	16.7.2 Exploratory Analysis 16.7.3 Exploratory Biomarker Analysis Biomarker assessments, to include collection of peripheral blood and skin biopsies, will be conducted in all patients...	16.8 Exploratory Analysis 16.8.1 Exploratory Biomarker and Pharmacodynamic Analyses Biomarker and pharmacodynamic assessments, to include collection of peripheral blood, skin biopsies, and tumor biopsies (*tumor biopsies optional*), will be conducted in all patients…

19.3 Protocol Amendment 3 dated 08-May-2018

- Tumor biopsies have been made mandatory; patients must be willing to undergo a total of 2 biopsies of a primary or metastatic tumor site(s) considered safely accessible for biopsy.
- AE grading will be based on the updated CTCAE v5 (previously CTCAE v4.03).
- Additional details regarding the process of eligibility confirmation have been provided.
- Details regarding the specific information to be collected regarding the patient's colorectal carcinoma history and prior therapy are no longer listed; however, there is no intended change in the scope of information to be obtained and documented in the patient's case report form.

- The body systems to be evaluated at the time of physical examination are no longer listed; however, there is no intended change in the scope or frequency of physical examinations to be conducted during this trial. It is emphasized that the skin is to be assessed at each visit.
- Analytes to be assessed in the event of abnormalities of creatine kinase are no longer listed; however, it is understood that best clinical judgment should be employed in evaluating patients with this or any other laboratory abnormality.
- Coagulation panel assessment and urinalysis have been added on Cycle 3/Day 1.
- ECGs may now be performed when patients are in a semi-recumbent (as well as a supine) position.
- Guidelines pertaining to the General Data Protection Regulation have been added.
- Tables have been updated based on changes described.
- Formatting adjustments, outline modifications, cross-reference links and link corrections, and other minor typographical corrections and slight wording changes are included.

Refer to **Table 32** for the changes in Protocol Amendment 3.

Table 32: Protocol Amendment 3

SECTION	ORIGINAL TEXT	NEW TEXT
1 Synopsis: Trial Objectives: Exploratory Objective 3.1.3 Exploratory Objective	To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood, skin biopsies, and tumor biopsies [tumor biopsies optional] to be collected). Tumor biopsies, if consent is obtained, will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models.*	To evaluate potential predictive and/or prognostic biomarkers of response to treatment *(peripheral blood, skin biopsies, and tumor biopsies to be collected). Tumor biopsies will be used to establish primary tumor and non-tumor cell lines, and patient-derived xenograft models.*
1 Synopsis: Trial Design: Design Summary	Third-Party Investigator Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization.	Designated Eligibility Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization.
1 Synopsis: Patient Selection: Key Eligibility Criteria	6. Patients with measurable disease according to RECIST v1.1	6. Patients with measurable disease according to RECIST v1.1, and willingness to undergo a total of 2 biopsies of a primary or metastatic tumor site(s) considered safely accessible for biopsy
1 Synopsis: Safety Assessments: ADA, PK, Genomic, and Pharmacodynamic Assessments	Pharmacodynamic Analyses (Specialty Lab) Peripheral blood, skin biopsies, and tumor biopsies (tumor biopsies optional) for potential predictive and/or prognostic biomarker assessment	Pharmacodynamic Analyses (Specialty Lab) Peripheral blood, skin biopsies, and tumor biopsies for potential predictive and/or prognostic biomarker assessment

Table 32: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
3.2 Trial Design Summary	Patient Population …Third-Party Investigator Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization. Study Assessments …Exploratory biomarker studies will be conducted in blood samples… in skin biopsies… and in tumor biopsies *(tumor biopsies optional)* obtained prior to and following Cycle 2 dosing.	Patient Population …Designated Eligibility Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization. Study Assessments …Exploratory biomarker studies will be conducted in blood samples… in skin biopsies… and in tumor biopsies obtained prior to and following Cycle 2 dosing.
4.2 Criteria for Inclusion	6. Patients with measurable disease according to RECIST v1.1 (Appendix 5)	6. Patients with measurable disease according to RECIST v1.1 (Appendix 5), and willingness to undergo a total of 2 biopsies of a primary or metastatic tumor site(s) considered safely accessible for biopsy
5.7 Dose Calculation	*Not applicable*	Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institutional procedures) as measured at the beginning of each dosing cycle (CxD1). Adjustments may be made in the event of lesser incremental changes in weight and/or more frequently at the site's discretion.
6.3.3 Submission of Patient Eligibility Information	Once the patient is screened and identified by the Investigator as meeting the study eligibility criteria, eligibility information must be submitted to the Sponsor (or designee) for review. The following information must be provided by the site: • Consent • Patient gender • Date of birth (or age), as allowed by local regulatory requirements • Date written informed consent was obtained • Confirmation of mCRC • Sites of measurable metastases • Confirmation of genomic analysis and patient TN mutation status • Confirmation of compliance with all inclusion/exclusion criteria • Brief description of prior therapy for the primary diagnosis, including dates of initiation and discontinuation as well as best response The following information may be requested of the site: • Patient weight (for dose calculation) • Date of screening • Current PS • Planned date of first dosing	Once the patient is screened and identified by the Investigator as meeting the study eligibility criteria, data supporting eligibility must be entered in the study electronic CRF for the Sponsor (or designee) to review. Information including: date written informed consent was obtained, demographics, diagnoses of primary malignancy and metastases, prior CRC treatments with systemic drug therapies including those specified in the protocol inclusion criteria will be required.

Table 32: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.3.4 Eligibility Confirmation	6.3.4 Authorization for Randomization Third-Party Investigator Reviewers and the Sponsor's Medical Monitor(s) (or designee) will review patient eligibility information provided, confirm eligibility, and authorize patients for randomization. Patients will be randomized in the order of confirmation of their eligibility and receipt of authorization.	6.3.4 Eligibility Confirmation The designated Eligibility Reviewers will review patient eligibility information provided and confirm eligibility. Upon confirmation, the site may proceed to request the randomized study treatment assignment for the patient.
6.3.5 Randomization	Authorized patients will be randomized in the ratio of 1:1:1 to Arm A (Sym004), Arm B (futuximab) or Arm C (modotuximab).	Eligible patients will be randomized in the ratio of 1:1:1 to Arm A (Sym004), Arm B (futuximab), or Arm C (modotuximab).
6.3.6 Patient Identification Code Assignment	Each patient to be randomized will be assigned a unique identification code. Identification codes will be assigned in chronological order, and will be concatenated to indicate relevant study information, including at minimum the participating trial site and the patient's order of randomization to the trial.	Each patient who signed informed consent will be assigned a unique identification code. Identification codes will be assigned in sequential order, and will be concatenated to indicate relevant study information, including at minimum the participating trial site and the patient's order of randomization to the trial.
6.3.7 Screen Failures	A list of patients failing screening, and the reason for ineligibility, will be maintained by the site on a Patient Screening Log or other similar document.	*Text removed*
7.1.5 History of mCRC	7.1.5 History of the Primary Malignancy (mCRC) *(Details of the primary malignancy to include:* - *diagnosis and histological/ cytological classification* - *date of initial diagnosis* - *date metastatic disease was identified* - *current sites of metastases* - *prior surgical procedures for the malignancy and dates* - *prior radiation therapy for the malignancy and dates* - *prior embolic therapy/procedures for the malignancy and dates* - *prior antineoplastic therapy, dates of treatments, numbers of cycles, indication of treatment [e.g. neoadjuvant, adjuvant, therapeutic for metastatic disease], reason for stopping, and best response to each therapy* - *prior anti-EGFR mAb therapy, dates of treatments, numbers of cycles, reason for stopping, and best response to each therapy* - *date of most recent disease progression)* • Screening	7.1.5 History of mCRC *(To include diagnoses of primary malignancy and metastases, prior CRC treatments with surgical procedures, radiation therapies, systemic drug therapies including those specified in the protocol inclusion criteria)* • Screening
7.2.5 Physical Examination	*(Complete at screening including height, weight, general appearance, skin, head, eyes, ears, nose, throat, neck/thyroid, chest [includes pulmonary assessment, breasts], cardiovascular [includes heart,*	*(To include measurement of height and weight at screening, and weight** during physical examinations thereafter; assessment of the skin is to be*

Table 32: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	*peripheral pulses] abdomen, musculoskeletal system, lymph nodes, neurologic and mental status; directed thereafter, must include weight**)*	*performed during each physical examination)*
7.2.7.2 Biochemistry Panel	****In the event of creatine kinase abnormalities while on study, perform isoenzyme analysis (to include at minimum CK-MB); in the event of ECG abnormalities while on study, perform isoenzyme analysis (to include at minimum CK-MB), serial troponins, and measurement of brain natriuretic peptide (BNP)*	*Text removed*
7.2.8 Electrocardiogram	*(To be evaluated locally; ECGs should be performed using the same calibrated instrument at each study center, and should be conducted after the patient has been supine for > 10 minutes.)* *(Patients with a QTc ≥ 500 msec should not be treated; dosing should be delayed.)* *(If abnormalities suggest new evidence of myocardial ischemia, perform isoenzyme analysis [to include at minimum CK-MB], serial troponins, and measurement of BNP)*	*(To be evaluated locally; ECGs should be performed using the same calibrated instrument at each study center, and should be conducted after the patient has been supine (or semi-recumbent) for > 10 minutes.)* *(Patients with a QTc ≥ 500 msec should not be treated; dosing should be delayed.)* *Text removed*
7.3 Specialty Assessments	Blood samples, skin biopsies, and tumor biopsies *(tumor biopsies optional)* will be taken according to the schedule shown (Table 5; Appendix 10).	Blood samples, skin biopsies, and tumor biopsies will be taken according to the schedule shown (Table 5; Appendix 10).
9.1 Criteria for Treatment Discontinuation	12. Site Terminated by the Sponsor	*Text removed*
15.1 Data Handling	Study data collection, processing, transfer, and reporting as well as handling of study personnel information will be in compliance with ICH E6(R2) GCP and all applicable data protection regulations.	Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).
15.5 Compliance with the General Data Protection Regulation	*Not applicable*	The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of

Table 32: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area), the parties will enter into the European Commission's standard contractual clauses between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.
16.8.1 Exploratory Biomarker and Pharmacodynamic Analyses	Biomarker and pharmacodynamic assessments, to include collection of peripheral blood, skin biopsies, and tumor biopsies *(tumor biopsies optional)*, will be conducted in all patients and will evaluate potential predictive and/or prognostic biomarkers of response to treatment…	Biomarker and pharmacodynamic assessments, to include collection of peripheral blood, skin biopsies, and tumor biopsies, will be conducted in all patients and will evaluate potential predictive and/or prognostic biomarkers of response to treatment…

19.4 Protocol Amendment 4 dated 02-Aug-2018

- Inclusion criterion 3 has been refined to indicate patients may have received other PD-1/PD-L1 pathway blockers to fulfill this prior treatment requirement.
- Clarified that 0.9% Sodium Chloride Injection, USP or local equivalent will be utilized as diluent.
- The End of Trial event has been more fully defined.
- Clarified final sample size.
- Formatting adjustments, minor typographical corrections, and slight wording changes are included.
- The synopsis and tables have been updated based on changes described, where applicable.

Refer to **Table 33** for the changes in Protocol Amendment 4.

Table 33: Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
3.2 Trial Design Summary	Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing including at the time of documented progression or study discontinuation for other reasons, in skin biopsies obtained prior to and following Cycle 1 and Cycle 2 dosing, and in tumor biopsies obtained prior to and following Cycle 2 dosing.	Exploratory biomarker studies will be conducted in blood samples obtained prior to and at intervals following dosing, including at the time of documented progression or study discontinuation for other reasons, in skin biopsies obtained prior to first dose and following Cycle 1 and Cycle 2 dosing, and in tumor biopsies obtained prior to first dose and following

Table 33: Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		Cycle 2 dosing.
4.2 Criteria for Inclusion	3. Patients with MSI-H/dMMR tumors must have received prior therapy with pembrolizumab or nivolumab (where approved in the country) and must have progressed on that therapy.	3. Patients with MSI-H/dMMR tumors must have received prior therapy with pembrolizumab, nivolumab, or other PD-1/PD-L1 pathway blocker, and must have progressed on that therapy.
5.6 Administration of IMPs	IMPs will be administered by IV infusion. An appropriate dose based on the patient's body weight is to be diluted with commercially available 0.9% sodium chloride (NaCl).	IMPs will be administered by IV infusion. An appropriate dose based on the patient's body weight is to be diluted with commercially available 0.9% Sodium Chloride Injection, USP or local equivalent.
5.8 Dose Preparation	• The total volume of IMP to be delivered will be withdrawn from the IMP vial(s) and added to a prefilled IV bag containing 0.9 % NaCl (following removal of an appropriate volume of saline, such that the final volume to be infused equals 500 mL for C1D1 loading dose infusions and 250 mL for subsequent infusions)	• The total volume of IMP to be delivered will be withdrawn from the IMP vial(s) and added to a prefilled IV bag containing 0.9 % Sodium Chloride Injection, USP or local equivalent (following removal of an appropriate volume of saline, such that the final volume to be infused equals 500 mL for C1D1 loading dose infusions and 250 mL for subsequent infusions)
6.2.2 Trial Duration	*Not applicable*	End of Trial: The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has been discontinued from study drug.
6.5.4.3 Diluent	Commercially available sterile 0.9% NaCl for IV infusion is to be used as the diluent.	Commercially available sterile 0.9% Sodium Chloride Injection, USP or local equivalent to be utilized for IV infusion as the diluent.
16.2 Sample Size Considerations	At the end of Stage 2, if greater than 20% rate is observed in either the futuximab or modotuximab Arms, an additional 10 patients may be added to obtain a more precise tumor shrinkage rate estimate and confidence interval (CI).	*Text has been removed*

19.5 Protocol Amendment 5 dated 18-Jan-2019

- Effective 20Dec2018, Sponsor decided to discontinue the trial for administrative reasons, and future accrual has been halted. As a result, the primary, secondary, and exploratory objectives are no longer applicable. Only clinical safety-related evaluations will continue to be conducted.
- ADA and samples for exploratory PK and PD assessments will not be collected. To date approximately 380 patients have been exposed to Sym004 (i.e., which includes the component antibodies futuximab and modotuximab); thus far immunogenicity or deleterious effects suggestive of development of ADA (serum sickness or related immune complex phenomena) have not been observed in the clinical setting. Therefore, in an effort to reduce overall blood collection from patients, it was considered acceptable to omit this assessment in this abbreviated study.

- Genomic samples for eligibility assessment will be obtained at prescreening and analyzed; however, post-dosing genomic samples for bioanalysis will not be collected.
- The schedule for tumor assessments has been modified and will be per institutional guidelines or Investigator discretion until confirmation of PD.
- A single center in the United States consented patients prior to the trial discontinuation date and will participate in the study going forward. Two (2) of 5 patients consented were determined to meet all eligibility criteria and have been enrolled in the study. Since only Sym004 has been shown to have potential clinical benefit, the protocol rules for cross-over and randomization were suspended; participating patients have been switched to or enrolled to receive Sym004.
- The statistical section has been modified to detail the planned reduction in data collection to information needed for safety reporting only.
- Reference to electronic data capture has been removed to allow the flexibility of using paper CRFs, if necessary.
- Formatting adjustments and administrative wording changes are included.
- The synopsis and tables have been updated based on changes described, where applicable.

Refer to **Table 34** for the changes in Protocol Amendment 5.

Table 34: Protocol Amendment 5

SECTION	ORIGINAL TEXT	NEW TEXT
2.4.1 Safety	As of January 2017, approximately 380 patients with solid tumors have been exposed to Sym004 in completed and ongoing Symphogen-sponsored trials, and 23 patients have been exposed to Sym004 in an investigator-initiated trial in patients with recurrent glioblastoma (Sym004-08).	As of January 2018, approximately 380 patients with solid tumors have been exposed to Sym004 in completed and ongoing Symphogen-sponsored trials, and 30 patients have been exposed to Sym004 in an investigator-initiated trial in patients with recurrent glioblastoma (Sym004-08).
3.1 Objectives	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as detailed below are no longer applicable. Only clinical safety-related evaluations will be conducted.
3.2 Trial Design Summary	*Not applicable*	As of Amendment 5: This amendment to the clinical trial protocol is based on the Sponsor's decision to discontinue the trial for administrative reasons, effective 20Dec2018; the intent to discontinue the trial was communicated to all active sites on this date. As a result, the original trial design as described below is no longer applicable, future accrual has been halted, and a reduction in the scope of non-safety-related assessments being conducted under this protocol has been implemented. Patients consented as of the trial discontinuation date, and determined to

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		meet study eligibility criteria, may be treated with IMP and may continue therapy until the occurrence of one of the following: unacceptable toxicity or other conditions preventing further administration, documented PD, or the patient's decision to withdraw. • Treated patients will be followed and assessed for only clinical safety-related concerns. • Of the Specialty Assessments initially planned: ADA and samples for exploratory PK and PD assessments (in peripheral blood, skin biopsies, and tumor biopsies) will not be collected; genomic samples for eligibility assessment were obtained at prescreening and analyzed, however post-dosing genomic samples will not be collected. • The frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion until confirmation of PD. The visit schedule for safety assessments will apply as specified elsewhere in this clinical trial protocol. Once IMP has been discontinued, an EOT visit will be performed within 7 to 10 days from the decision to withdraw treatment, and a 1M FUP visit will be performed 30 days (+7 days) following the last dose. The pre-Amendment 5 trial design was as follows:
4.1 Number of Patients	*Not applicable*	As of Amendment 5: As of the trial discontinuation date (20Dec2018), a single center in the United States had consented and screened patients. Two (2) of 5 patients screened were determined to be eligible for participation and both were enrolled in the study. The total number of sites planned will not be participating; the total number of patients planned will not be enrolled.
4.2 Criteria for Inclusion	*Not applicable*	As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; however, patients consented prior to the effective date will be required to meet the following inclusion criteria:
4.3 Criteria for Exclusion	*Not applicable*	As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; however, patients consented prior to the effective date will be required to meet the following exclusion criteria:
6.2.1 Recruitment Period	*Not applicable*	As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted. Previous recruitment projections were as follows:
6.2.2 Trial Duration	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the primary, secondary, and exploratory

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		objectives as previously described are no longer applicable. Planned efficacy analyses, as well as planned specialty analyses (including ADA as well as exploratory PK and PD analyses) will not be performed. Only clinical safety-related analyses will be conducted; data cut-off will occur and safety analyses will be performed at the end of trial.
6.2.3 Trial Closure	*Not applicable*	As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients will not be enrolled. Once the 2 patients entered to the trial have discontinued treatment and all required safety follow-up has been completed, the trial will be closed. The pre-Amendment 5 trial closure plan detailed below will not be followed.
6.3.3 Submission of Patient Eligibility Information	Once the patient is screened and identified by the Investigator as meeting the study eligibility criteria, data supporting eligibility must be entered in the study electronic CRF for the Sponsor (or designee) to review.	Once the patient is screened and identified by the Investigator as meeting the study eligibility criteria, data supporting eligibility must be entered in the study CRF for the Sponsor (or designee) to review.
6.3.5 Randomization	*Not applicable*	As of Amendment 5: As of the trial discontinuation date (20Dec2018), 5 patients had provided written consent for trial participation; following screening, 2 were determined to be eligible. The first patient was deemed eligible prior to the trial discontinuation date and was randomized to Arm B (futuximab). The second patient was deemed eligible after the trial discontinuation date and although randomized to Arm B (futuximab), per Sponsor decision was enrolled to Arm A to receive Sym004. The pre-Amendment 5 randomization plan detailed below will not be followed.
6.5.2 Patient Availability	*Not applicable*	*As of Amendment 5: PK sampling has been omitted; the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion until confirmation of PD.
6.5.4 Administration Details	*Not applicable*	As of Amendment 5: Two (2) patients screened and determined to be eligible have been treated with IMP. The first patient deemed eligible prior to the trial discontinuation date (20Dec2018) was randomized to Arm B (futuximab) and crossed over to Arm A (Sym004) at the EOC1 per Sponsor decision; the second patient deemed eligible after the trial discontinuation date was randomized to Arm B (futuximab), however per Sponsor decision was enrolled to Arm A to receive Sym004. With this amendment, the doses of IMP to be delivered remain unchanged; however, the pre-Amendment 5 crossover dose plan as detailed below is no longer in effect.

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.7.3 Treatment after Cycle 2	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the frequency of disease status evaluations will be per either institutional guidelines or Investigator discretion. Enrolled patients (2 total) have been either crossed over to receive or are receiving Sym004, and may continue to receive Sym004 until confirmation of PD. The pre-Amendment 5 plan for continued treatment after Cycle 2 as detailed below will not be followed.
7 Study Assessments	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), the original trial design is no longer applicable. Only clinical safety-related evaluations will be conducted. The visit schedule for the treatment period will apply as specified below, with indicated exceptions. Once IMP has been discontinued, an EOT visit will be performed within 7 to 10 days from the decision to withdraw treatment, and a 1M FUP visit will be performed 30 days (+7 days) following the last dose. The pre-Amendment 5 study assessment schedule was as follows:
7.3 Specialty Assessments	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related evaluations will be conducted. Of the Specialty Assessments detailed below, ADA and samples for exploratory PK and PD assessments (in peripheral blood, skin biopsies, and tumor biopsies) will not be collected. Genomic samples for eligibility assessment were obtained at prescreening and analyzed; however post-dosing genomic samples will not be collected. Note: Samples for ADA and samples for exploratory PK and PD assessments, if collected prior to implementation of this amendment, will not be analyzed and will be destroyed. The pre-Amendment 5 specialty assessments were as follows:
7.3.1 Immunogenicity Assessment (Specialty Laboratory)	*Not applicable*	As of Amendment 5: Immunogenicity assessments have been omitted. Immunogenicity assessments were initially planned as follows:
7.3.2 Exploratory Pharmacokinetic Assessment (Specialty Laboratory)	*Not applicable*	As of Amendment 5: Exploratory PK assessments have been omitted. Exploratory PK assessments were initially planned as follows:

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.3.3 Genomic Analysis in Peripheral Blood (Specialty Laboratory)	*Not applicable*	As of Amendment 5: Genomic assessments have been omitted with the exception of prescreening genomic sampling for eligibility assessment (*). Genomic assessments were initially planned as follows:
7.3.4 Pharmacodynamic Analyses (Specialty Laboratory)	*Not applicable*	As of Amendment 5: Pharmacodynamic assessments (including collection of peripheral blood, skin biopsies, and tumor biopsies) have been omitted. Pharmacodynamic assessments were initially planned as follows:
7.4.1 Diagnostic Imaging for Tumor Measurements (Local Assessment)	• Screening • EOC2 and every even-numbered cycle thereafter (i.e., approximately every 8 weeks)* • EOT (if > 6 weeks since previous assessment) • As clinically indicated (in the event of suspected PD) *End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.	• Screening • As of Amendment 5: frequency per either institutional guidelines or Investigator discretion until confirmation of PD
7.4.2 Response Assessment (Local Assessment)	• EOC2 and every even-numbered cycle thereafter (i.e., approximately every 8 weeks)* • EOT (if > 6 weeks since previous assessment) • As clinically indicated (in the event of suspected PD) *End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.	• As of Amendment 5: frequency per either institutional guidelines or Investigator discretion until confirmation of PD
14.8 Recording of Data	Clinical trial data for this study will be captured in an electronic format. Electronic data capture (EDC) services will be provided by a vendor to be determined by the Sponsor. The Investigator agrees to provide all information requested in the CRF in an accurate manner according to instructions provided. CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be identified and tracked by audit trails within the EDC system. Data must be entered into CRFs in a timely fashion.	Clinical trial data for this study will be captured in a CRF. The Investigator agrees to provide all information requested in the CRF in an accurate manner according to instructions provided. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be identified and tracked. Data must be entered into CRFs in a timely fashion.
15.3 Data Processing	Once recorded within the electronic CRF, study data will pass through a set of preprogrammed data validation checks designed to identify inconsistencies and other data errors, and also will undergo an additional study-specific data review process, as stated above in Section 15.2. Data	Once recorded within the CRF, study data will be checked to identify inconsistencies and other data errors, and also will undergo an additional study-specific data review process, as stated above in Section 15.2. Data issues will be queried and query resolutions will be documented.

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	issues will be queried via the EDC system and query resolutions will be documented. Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g., imports of laboratory results) will follow vendor(s) SOPs. Transfer of such data from vendor(s) to Sponsor (or designee) will be handled according to vendor(s) data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations. Database Lock will occur upon reaching the predefined data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control procedures and quality assurance procedures. Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.	Entry and processing of data other than those directly recorded on CRFs by trial sites (e.g., imports of laboratory results) will follow vendor(s) SOPs. Transfer of such data from vendor(s) to Sponsor (or designee) will be handled according to vendor(s) data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations. Database Lock will occur upon reaching the predefined data cut-off and completion of Sponsor's (or designee's) quality control procedures and quality assurance procedures. Portable Document Format (PDF) files of the CRFs will be provided to the Investigator at the end of the trial.
15.4 Clinical Trial Report	A final integrated clinical/statistical Clinical Trial Report (CTR) will be prepared upon reaching the predefined data cut-off for primary analysis (i.e., all patients complete their first on-study tumor assessment).	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial for administrative reasons (effective 20Dec2018), the primary, secondary, and exploratory objectives as previously described are no longer applicable. Only clinical safety-related evaluations will be conducted. An abbreviated CTR will be prepared upon completion of the trial rather than the full integrated report described below. A final integrated clinical/statistical trial report will be prepared upon reaching the predefined data cut-off for primary analysis (i.e., all patients complete their first on-study tumor assessment).
16.2 Sample Size Considerations	*Not applicable*	As of Amendment 5: Effective 20Dec2018, accrual to this trial has been halted; the total planned number of patients will not be enrolled. Two (2) patients consented prior to the trial discontinuation date and subsequently determined to be eligible have been entered to the study. The pre-Amendment 5 sample size considerations detailed below are no longer valid.
16.3 Analysis Sets	• PK Analysis Set: All patients in the AT analysis set who receive any amount of their assigned dose of the IMPs, Sym004, futuximab or modotuximab, have a measurable concentration of at least one of the IMPs for at least one timepoint after the first dose, with no significant protocol deviations that may impact the data.	• PK Analysis Set*:… *As of Amendment 5: PK analysis will not be performed, therefore the PK analysis set is no longer applicable.

Table 34: Protocol Amendment 5		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
16.4 Trial Endpoints	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The pre-Amendment 5 efficacy and exploratory endpoints as detailed below are no longer valid and will not be analyzed.
16.4.1 Primary Efficacy Endpoint	*Not applicable*	*"(omitted as of Amendment 5)" added to section heading*
16.4.2 Exploratory Endpoints and Analyses	*Not applicable*	*"(omitted as of Amendment 5)" added to section heading*
16.5 Statistical Analysis	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only data from clinical safety-related evaluations will be summarized. Since only 2 patients are being treated in the study, the available baseline and safety data for these two patients will be presented as either patient profiles or patient listings. The pre-Amendment 5 full statistical analysis as detailed below will not be performed.
16.6 Primary Analysis	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned efficacy analyses as detailed below will not be performed.
16.8 Exploratory Analysis	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned exploratory analyses as detailed below will not be performed.
16.10 Interim Analysis	*Not applicable*	As of Amendment 5: Due to the Sponsor's decision to discontinue the trial (effective 20Dec2018), only clinical safety-related analyses will be conducted. The planned interim analyses as detailed below will not be performed.