CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination With Bevacizumab and FOLFIRI Versus Bevacizumab and FOLFIRI in Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)
Short Title:	Study of Magrolimab Given Together With FOLFIRI/BEV in Patients With Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	117687
EU CT Number:	2022-500177-13-00
ClinicalTrials.gov Identifier:	NCT05330429
Indication:	Metastatic Colorectal Cancer (mCRC)
Protocol ID:	GS-US-587-6156
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 5 — 31 October 2023
Amendment History	Original: — 28 September 2021 Amendment 1: — 27 January 2022 Amendment 2: — 10 March 2022 Amendment 2.1-CTIS: — 12 July 2022 Amendment 3: — 25 October 2022 Amendment 3.1-CTIS — 26 October 2022 Amendment 4 — 21 June 2023 Amendment 5 — 31 October 2023 High-level summaries of the histories of amendments are provided in Appendix 13.

Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 12.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are considered noninvestigational new drug application sites.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-fluorouracil
CCI	[redacted]
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CBC	complete blood count
CD47	cluster of differentiation 47
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical trials information system
CTR	Clinical Trials Regulation
CYP	cytochrome P450 enzyme
CCI	[redacted]
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
dMMR	mismatch repair deficiency
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire
ERBB	v-erb-b2 erythroblastic leukemia viral oncogene homolog

EQ-5D	EuroQol (5 dimensions)
EQ-5D-5L	5-level EuroQol 5 dimensions
EQ-VAS	EuroQol visual analogue scale
EU	European Union
EU CT	European Union Clinical Trials
FACT	Functional Assessment of Cancer Therapy
Fc	crystallizable fragment
FCSI	FACT Colorectal Symptom Index
FDA	Food and Drug Administration
FOLFIRI	5-fluorouracil, irinotecan, and leucovorin
FOLFOX	5-fluorouracil, oxaliplatin, and leucovorin
GCP	Good Clinical Practice
GDRC	Gilead Data Review Committee
Gilead	Gilead Sciences/Gilead Sciences, Inc.
PS	Patient Safety
Hb	hemoglobin
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
Ig	immunoglobulin
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
CCI	[redacted]
LV	leucovorin
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCRC	metastatic colorectal cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

MID	minimum important difference
MNS	any of the blood groups M, N, and S comprising the MNS system
MOA	mechanism of action
MRI	magnetic resonance imaging
MSI-H	high microsatellite instability
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NRAS	neuroblastoma RAS viral oncogene homolog
ORR	objective response rate
OS	overall survival
CCI	[redacted]
PD	pharmacodynamic(s)
PD-1	programmed cell death-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial remission
PRO	patient-reported outcome
CCI	[redacted]
[redacted]	[redacted]
Q2W	every 2 weeks
RANKL	receptor activator of nuclear factor kappa B ligand
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
Rh	rhesus
RNA	ribonucleic acid
RO	receptor occupancy
ROW	rest of world
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIRPα	signal regulatory protein alpha
SOC	standard of care
SRT	Safety Review Team
SSR	special situation report
TRK	tropomyosin receptor kinase
ULN	upper limit of normal
US, USA	United States, United States of America
VBG	venous blood gas
VEGFR	vascular endothelial growth factor receptor

VEGF	vascular endothelial growth factor
w/v	weight-to-volume ratio
WBC	white blood cell

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title: A Phase 2, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination With Bevacizumab and FOLFIRI Versus Bevacizumab and FOLFIRI in Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)

Short Title: Study of Magrolimab Given Together With FOLFIRI/BEV in Patients With Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)

Regulatory Agency Identifier Number(s):

IND Number: 117687
EU CT Number: 2022-500177-13-00
ClinicalTrials.gov Identifier: NCT05330429

Study Centers Planned:

Approximately 45 centers worldwide

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
Safety Run-in Cohort: • To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of magrolimab in combination with bevacizumab and FOLFIRI (5-fluorouracil [5-FU], irinotecan, and leucovorin [LV]) in previously treated patients with advanced inoperable metastatic colorectal cancer (mCRC) Randomized Cohort: • To evaluate the efficacy of magrolimab in combination with bevacizumab and FOLFIRI in mCRC as determined by progression-free survival (PFS) by investigator assessment	Safety Run-in Cohort: • Incidence of dose-limiting toxicities (DLTs), and adverse events (AEs) and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Randomized Cohort: • PFS, defined as the time from the date of randomization until the earliest date of documented disease progression as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V1.1), or death from any cause, whichever occurs first
Secondary Objectives	**Secondary Endpoints**
Randomized Cohort: • To evaluate objective response rate (ORR) by investigator assessment • To evaluate additional measures of efficacy of magrolimab in combination with bevacizumab and FOLFIRI, including duration of response (DOR) and overall survival (OS)	Randomized Cohort: • Confirmed ORR, defined as the proportion of patients with complete response (CR) or partial response (PR) on 2 consecutive assessments, at least 28 days apart, as determined by investigator assessment using RECIST V1.1

• To evaluate patient-reported outcomes (PRO)/quality-of-life measures for the Randomized Cohort in mCRC with magrolimab in combination with bevacizumab and FOLFIRI Safety Run-in and Randomized Cohorts: • To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with bevacizumab and FOLFIRI	• DOR, defined as time from first documentation of CR or PR to the earliest date of documented disease progression as determined by investigator assessment, per RECIST V1.1, or death from any cause, whichever occurs first • OS, defined as time from date of randomization to death from any cause • PRO assessments (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire [EORTC-QLQ-C30], the 5-level EuroQol 5 dimensions questionnaire [EQ-5D-5L]) scores, and Functional Assessment of Cancer Therapy [FACT] Colorectal Symptom Index [FCSI] Safety Run-in and Randomized Cohorts: • Magrolimab concentration versus time and antidrug antibodies (ADA) to magrolimab
Exploratory Objectives	**Exploratory Endpoints**
• CCI [redacted]	[redacted]

Study Design: A schematic diagram of the study is provided in Figure 1.

This is a Phase 2, randomized, open-label, multicenter study to evaluate magrolimab in combination with bevacizumab and FOLFIRI in previously treated patients with advanced inoperable mCRC CCI [redacted] who do not harbor BRAF V600E mutations or high microsatellite instability (MSI-H).

This study will consist of the following 2 cohorts:

- **Safety Run-in Cohort:** magrolimab in combination with bevacizumab and FOLFIRI in previously treated patients with advanced inoperable mCRC

After completion of the Safety Run-in Cohort, the Randomized Cohort will be open to enrollment.

- **Randomized Cohort:** magrolimab in combination with bevacizumab and FOLFIRI (Experimental Arm A) versus bevacizumab and FOLFIRI (Control Arm B) in previously treated patients with advanced inoperable mCRC

Safety Run-in Cohort: approximately 6 patients will be enrolled in the Safety Run-in Cohort at a starting dose level. A DLT-assessment period of 28 days will occur.

Although no dose-dependent toxicities have been observed with magrolimab, in order to preserve the efficacious doses of the combination partner drugs, dose de-escalation will take place for magrolimab as follows:

- If 2 or less of 6 DLT-evaluable patients experience a DLT during the first 28 days, enrollment into the Randomized Cohort will begin at this dose level as the RP2D.
- If more than 2 patients experience at least one DLT during the first 28 days, enrollment at the current dose level will immediately stop and dose de-escalation will occur. Up to 6 other patients will then be enrolled and evaluated at a lower dose level in the same manner.
  - Once the RP2D is determined, the sponsor will open the Randomized Cohort.

Approximately 6 patients will be enrolled in the Safety Run-in Cohort. Additional patients may be added to the Safety Run-in Cohort or enrolled in a dose de-escalation cohort.

Dose-Limiting Toxicity Assessment Period for the Safety Run-in Cohort: The DLT-assessment period will be the first 28 days and applies to the Safety Run-in Cohort. Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT-assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completes at least 3 infusions of magrolimab and at least 2 doses of bevacizumab and FOLFIRI in the Safety Run-in Cohort.

If a patient experiences a DLT during the DLT-assessment period, the patient will discontinue treatment.

Patients who are not evaluable for DLT assessment in the Safety Run-in Cohort will be replaced.

Randomized Cohort: Once the Safety Run-in Cohort is completed and the RP2D for magrolimab in combination with bevacizumab and FOLFIRI is determined, the sponsor will open the Randomized Cohort. In this open-label, randomized, 2-arm study, patients with mCRC will be randomized in a 2:1 ratio to receive either magrolimab in combination with bevacizumab and FOLFIRI (Experimental Arm A) or bevacizumab and FOLFIRI (Control Arm B). The primary efficacy assessment will be investigator assessed PFS, with the primary analysis to occur after 85 PFS events. Stratification factors for randomization include the following: (1) Kirsten rat sarcoma (KRAS) mutation/unknown versus wild-type status, (2) geographic region (United States [US] versus European Union [EU]/rest of world [ROW]), (3) presence versus absence of liver metastases.

Number of Patients Planned:

Approximately 135 patients

- Safety Run-in Cohort: approximately 6 to 18 patients. Additional patients could be enrolled in this cohort or in dose de-escalation cohorts.
- Randomized Cohort: approximately 117 patients in Arms A and B.

Target Population: Previously treated patients with advanced inoperable mCRC who have progressed CCI [redacted]

Duration of Treatment: All patients will continue study treatment unless they meet study treatment discontinuation criteria. Survival follow-up will be conducted via a phone call CCI [redacted] Duration of survival follow-up will be limited to CCI .

Diagnosis and Main Eligibility Criteria:

- Male or female, at least 18 years of age.
- Histologically or cytologically confirmed adenocarcinoma originating in the colon or rectum (excluding appendiceal and anal canal cancers) who have progressed on or after 1 prior systemic therapy in the setting where curative resection is not indicated. This therapy must have included chemotherapy based on 5-FU or capecitabine with oxaliplatin and either bevacizumab, or for patients with RAS wild-type and left-sided tumors, bevacizumab, cetuximab, or panitumumab.
- Measurable disease (at least 1 measurable metastatic lesion by RECIST V1.1 criteria, with lesion not located in a previous field of radiation). Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.
- Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Procedures/Frequency: The schedule of study procedures are presented in Table 1, Table 2, and Table 3.

Test Product, Dose, and Mode of Administration:

- Magrolimab 1 mg/kg intravenous (IV)
- Magrolimab 15 mg/kg IV
- Magrolimab 20 mg/kg IV
- Magrolimab 30 mg/kg IV

In combination with bevacizumab:

- Bevacizumab: 5 mg/kg every 2 weeks

In combination with FOLFIRI. An example is provided below:

- Irinotecan 180 mg/m^2 Day 1
- LV 400 mg/m^2 over 2 hours Day 1
- 5-FU 400 mg/m^2 bolus Day 1, followed by 2400 mg/m^2 over 46 hours, continuous infusion

Reference Therapy, Dose, and Mode of Administration:

In combination with bevacizumab:

- Bevacizumab: 5 mg/kg every 2 weeks

In combination with FOLFIRI. An example is provided below.

- Irinotecan 180 mg/m^2 Day 1
- LV 400 mg/m^2 over 2 hours Day 1
- 5-FU 400 mg/m^2 bolus Day 1, followed by 2400 mg/m^2 over 46 hours, continuous infusion

Statistical Methods:

Analysis Data Sets

The DLT-Evaluable Analysis Set for the Safety Run-in Cohort will include all patients who meet one of the following criteria in the DLT-evaluable period:

- Patient experienced a DLT at any time after initiation of the first infusion of magrolimab
- Patient did not experience a DLT and completes at least 3 infusions of magrolimab and at least 2 doses of bevacizumab and FOLFIRI in the Safety Run-in Cohort.

For the Safety Run-in Cohort, the modified Intent-to-Treat (ITT) and Safety Analysis Sets will include all patients who received at least 1 dose of any study drug.

For the Randomized Cohort, the ITT Analysis Set will include all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified. The Safety Analysis Set will include all randomized patients who received at least 1 dose of any study drug, with treatment assignments designated according to the actual treatment received.

The PK Analysis Set will include all patients who received any amount of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

The Immunogenicity Analysis Set will include all patients who received any amount of magrolimab and had at least 1 evaluable ADA test result.

The Biomarker Analysis Set includes all patients who received any study drug and have at least 1 evaluable biomarker measurement available. This will be the primary analysis set for all biomarker data analyses.

Dose Determination Analysis

For the purposes of making the dose de-escalation decisions for the Safety Run-in Cohort, dose determination analyses of relevant safety data focusing on DLTs and overall safety profile will be conducted by a safety review team after all patients have completed the required DLT-assessment period. Safety assessments (eg, AEs, electrocardiogram, laboratory results) will be displayed to facilitate the dose de-escalation decisions.

Efficacy Analysis

For the Randomized Cohort, PFS by investigator assessment will be analyzed using Kaplan-Meier (KM) methods. Patients who did not have documented disease progression or death will be censored at the date of their last response assessment during the study with documentation of no disease progression. The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided

along with the corresponding 95% CI. A log-rank test stratified by the randomization factors will be used to compare treatment difference in PFS. A stratified Cox proportional hazard regression model will be used to estimate the hazard ratio (HR) and its 2-sided 95% CI.

Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications in the Safety Analysis Set. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized.

Sample Size Calculation

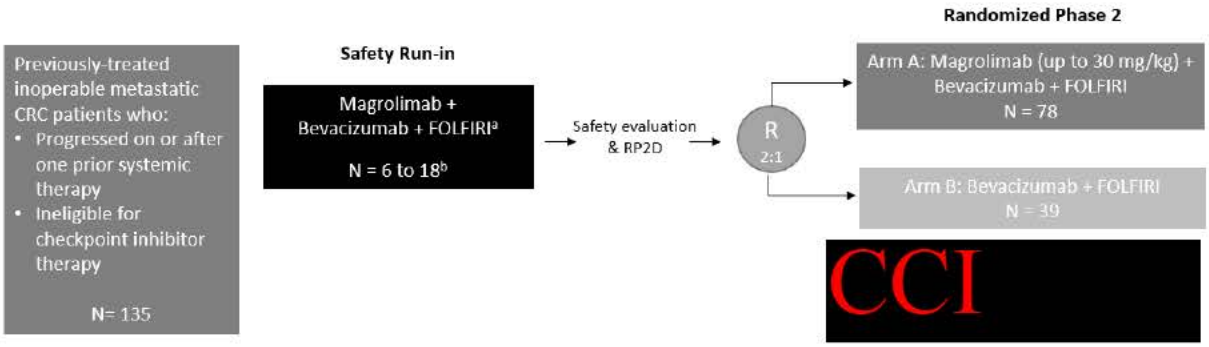
For the Randomized Cohort Arm A and Control Arm B, using an unstratified log-rank test, a total of 85 PFS events provides 73% power at a 1-sided alpha of 0.15 to detect a HR of 0.69 (assuming median PFS of ≥ 8.3 months compared with a control arm median PFS of 5.7 months). Assuming an accrual period of 10 months, a minimum follow-up time of 10 months, and a 5% annual drop-out rate, 117 total patients (78 patients in experimental arm and 39 patients in the control arm) would be required to obtain 85 PFS events.

Power calculations were performed using EAST 6.5.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SCHEMA

Figure 1. Study Schema



5-FU = 5-fluorouracil; CRC = colorectal cancer; FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; CCI ; RP2D = recommended Phase 2 dose; CCI

a FOLFIRI: irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2.

b Additional patients may be enrolled in the safety run-in or in dose de-escalation cohorts.

STUDY PROCEDURES TABLES

Table 1. Study Procedures Table – Screening Assessments

Assessment	Day −30 to −1
Informed consent[a]	X
Demographics	X
Medical and cancer history	X
ECOG	X
Vital signs, height, and weight	X
Complete physical examination	X
ECG (single)	X
CCI	
Pregnancy test[b]	X
CCI	
Hematology[d]	X
Serum or plasma chemistry[e]	X
Coagulation[f]	X
CCI	
Urinalysis[h]	X
Tumor imaging[i]	X
Tumor biopsy	X
Serious adverse events related to protocol-mandated procedures	X
Concomitant medications	X
CCI	
Randomization[a]	X
IRT registration	X

CCI
CT = computed tomography; CCI DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; IRT = interactive response technology; MRI = magnetic resonance imaging; CCI

a Screening must be completed before randomization. CCI .

b Serum pregnancy test will be conducted for women of childbearing potential at screening. Screening pregnancy test may be used as the Day 1 test if performed within 72 hours of first dose.

c CCI

d A complete blood count with CCI .

e Serum will be collected to test for uric acid and phosphorus.

f CCI

g Samples may be collected and analyzed prior to screening, see Section 6.2.1.

h Reflex microscopic testing based on other abnormalities.

i CT/MRI will be performed per Section 6.3.10.

Table 2. Study Procedures Table – Treatment Period

	CCI
Visit Window (Days)	
Cycle Day	
ECOG[b]	
Vital signs and weight[c]	
Symptom-directed physical examination[d]	
Pregnancy test[d, e]	
Hematology[d, f]	
CCI	
Serum or plasma chemistry[d, g]	
Tumor imaging[h]	
Tumor biopsy	
Adverse events	
Concomitant medications	
PRO assessment: EORTC-QLQ-C30, EQ-5D-5L, and FACT Colorectal Symptom Index[b,d] (Randomized Cohort only)	

CCI

	CCI
Visit Window (Days)	
Cycle Day	
CCI	
IRT registration[u]	
Magrolimab, bevacizumab, and FOLFIRI dosing[v]	

CCI ; CEA = carcinoembryonic antigen; CT = computed tomography; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire; EQ-5D-5L = 5-level EuroQol 5 dimensions; FACT = Functional Assessment of Cancer Therapy; FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; IRT = interactive response technology; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; CCI PK = pharmacokinetic(s); PRO = patient-reported outcome; CCI RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; CCI
Refer to Section 6.3.9 for complete list of analytes to be tested. All laboratory assessments are to be tested at the central laboratory per protocol or laboratory manual, unless local laboratory testing has been specified.

CCI

Table 3. Study Procedures Table – Posttreatment Assessments

	EOT Visit	Safety Follow-up Visit/Call (Telephone)[a]	Preprogression Visit[b]	Survival Follow-up (Telephone)
Visit Window	**Within CCI After Last Dose or EOT Decision**	**CCI After Last Dose**	**After Safety Follow-up Until Disease Progression**	**Every CCI After Safety Follow-up**
Urine or serum pregnancy test[c]	CCI			
Hematology[d]				
Serum or plasma chemistry[e]				
Pharmacokinetics				
CCI				
Tumor imaging for response assessment[j]				
ECOG				
Vital signs				
Symptom-directed physical examination				
Adverse events[k]				
Concomitant medications				
New anticancer therapy[l]				
Survival follow-up				

ADA = antidrug antibody; AE = adverse event; CT = computed tomography; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site.

b This will only apply for patients who stop study treatment in the absence of progression of disease per RECIST V1.1 and will continue to have tumor imaging. Details on the tumor imaging schedule are provided in footnote j. Preprogression visits will be completed first before proceeding to survival follow-up.

[redacted]

j Tumor imaging at EOT visit not required if performed within the last 30 days or progressive disease per RECIST V1.1 has been documented. CT/MRI will be performed per Section 6.3.10. For patients who stop study treatment in the absence of progression of disease per RECIST V1.1 (eg, experienced unexpected toxicity), scans should continue to be collected approximately every CCI until disease progression or initiation of systemic antitumor therapy other than the study treatment, whichever is earlier.

k Report all AEs through the safety follow-up visit/call, and any treatment-related SAEs thereafter.

l Collect new anticancer therapy data following the last dose of study treatment until the end of survival follow-up.

m Survival follow-up will be conducted via a phone call every CCI [redacted]. Duration of survival follow-up will be limited to CCI .

1. INTRODUCTION

1.1. Background

Metastatic colorectal adenocarcinoma ranks as the second most lethal cancer and the third most prevalent malignant tumor worldwide. In 2018, 1.8 million new cases and 881,000 deaths were reported, which accounted for nearly 10% of new cancer cases and deaths worldwide {Bray 2018}. The number of new cases is expected to increase to nearly 2.5 million in 2035 {Dekker 2019}. In the United States (US), metastatic colorectal cancer (mCRC) is the second leading cause of cancer deaths {Siegel 2018}. In 2020, 148,000 new diagnoses and 53,200 deaths were reported, including 17,930 cases and 3,640 deaths in individuals younger than 50 years of age. The 5-year survival rate is approximately 15% {Surveillance Epidemiology and End Results (SEER) 2021}. Although screening strategies and new treatment modalities have started to reduce the overall CRC death rate, the development of advanced metastatic disease is still associated with poor long-term survival. Recent data has demonstrated a continued decline in incidence and mortality in patients at least 65 years of age but a converse increase among those less than 65 years of age. The etiology of this phenomenon has yet to be determined and differences in genetics may be a factor.

Colorectal cancer is a heterogeneous disease complicated by the common occurrence of several molecular alterations comprising the epidermal growth factor receptor (EGFR) pathway, including mutations in Kirsten rat sarcoma (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF [V600E]), and in the human epidermal growth factor receptor 2 (HER2) and MET receptors. Other molecular alterations include DNA damage repair mechanisms and rare kinase fusions. Moreover, tumor sidedness is associated with distinct clinical and biological characteristics. Right-sided CRC is more common in women, and associated with Lynch syndrome, mitogen-activated protein kinase (MAPK)-signaling, high microsatellite instability (MSI-H), deficiency of mismatch repair genes, CpG island methylation, and KRAS and BRAF mutations. Left-sided CRC is more common in men, and associated with familial adenomatous polyposis syndrome, wingless-related integration site (Wnt) and EGFR signaling, chromosomal instability, v-erb-b2 erythroblastic leukemia viral oncogene homolog 1 (ERBB1) and ERBB2 amplifications, APC, p53, and NRAS mutations. These alterations represent oncogenic drivers that may coexist in the same tumor with other primary and acquired alterations via a clonal selection process.

Advances have been made in the therapy of CRC in targeted subgroups with specific mutational profiles. However, resistance to these targeted agents as well as standard chemotherapies based on specific molecular alterations have confounded treatment. Increasingly, enhanced knowledge about tumor biology is driving therapeutic decision-making. Optimal combinations and sequencing of these agents is continuing to evolve. Known biologic drugs that are active against mCRC include agents targeting vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs), EGFR, BRAF V600E, HER2, immunotherapy using immune checkpoint inhibitors, and tropomyosin receptor kinase (TRK) inhibitors. Biomarkers have been defined for patients who are candidates for agents targeting EGFR, HER2, TRK fusions, and for immunotherapy, but are not yet defined for other agents.

Systemic chemotherapy in combination with anti-EGFR antibodies such as cetuximab and panitumumab have significantly improved prognosis in KRAS wild-type patients {Lee 2015}. In addition, patients with MSI-H have demonstrated impressive responses to checkpoint inhibitors such as the anti–programmed cell death-1 (PD-1) agent pembrolizumab {Le 2015, Overman 2016}, but this represents only a subset of this tumor type (10% to 15% at diagnosis). On the other hand, certain subsets of patients such as those with KRAS mutations, which comprise over 40% of CRCs {Vaughn 2011}, do not respond to anti-EGFR antibody therapies {Allegra 2009}. Patients with KRAS-mutant mCRC have a poorer prognosis while having limited available therapies. For the majority of patients who are ineligible or unable to derive benefit from novel targeted therapies or immunotherapies, standard of care (SOC) doublet or triplet chemotherapy based regimens that are associated with systemic toxicity, unsatisfying response rates, unpredictable innate and acquired resistance, as well as low tumor-specific selectivity are the only available treatment options. Therefore, significant and clinically relevant improvements in efficacy that advance the treatment landscape are still needed to address this high unmet medical need in patients with CRC.

1.2. Information About Magrolimab

CD47 is a key molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic “eat me” signals {Jaiswal 2009, Majeti 2009}. The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal {Chao 2012}. Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint {Chao 2012}. Increased CD47 expression was identified first on leukemic stem cells in human acute myeloid leukemia (AML) {Majeti 2009}, and since then it has been found that CD47 expression is increased on the surface of cancer cells in a diverse set of human tumor types.

Magrolimab is a recombinant humanized anti-CD47 monoclonal antibody that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells {Liu 2015}. The activity of magrolimab is primarily dependent on blocking CD47 binding to signal regulatory protein alpha (SIRPα) and not on the recruitment of crystallizable fragment (Fc)-dependent effector functions, although the presence of the immunoglobulin (Ig) G4 Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells {Liu 2015}. Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

1.2.1. General Information

For further information on magrolimab, including information on the following, refer to the current investigator's brochure (IB) for magrolimab:

- Nonclinical pharmacology
- Pharmacokinetics (PK) and product metabolism in animals
- Nonclinical toxicology
- Clinical experience

1.3. Information About Bevacizumab, FOLFIRI, and Study Auxiliary Medicinal Products

1.3.1. Role of Chemotherapy in Metastatic Colorectal Cancer

Despite well-known genetic differences in the disease, chemotherapy treatment of CRC is largely uniform. Patients with newly diagnosed mCRC are treated with fluoropyrimidine based regimens, such as FOLFOX (5-fluorouracil [5-FU], oxaliplatin, and leucovorin [LV]), CAPOX (capecitabine and oxaliplatin), or FOLFIRI (5-FU, irinotecan, and LV) alone or in combination with therapies that target VEGF or EGFR signaling.

A meta-analysis of 7 Phase 3 studies evaluating therapeutic regimens associating 5-FU/LV, oxaliplatin, and irinotecan demonstrated that patients receiving the 3 drugs, regardless of the first doublet regimen used, exhibited prolonged survival compared with patients receiving a single doublet {Grothey 2004}. However, capecitabine exhibited equivalence to 5-FU and represents a well-tolerated alternative association for irinotecan or oxaliplatin. After disease progression, a crossover second-line regimen associating fluoropyrimidine/oxaliplatin or fluoropyrimidine/irinotecan with another agent exhibited satisfactory response rates along with disease stabilized over a period of several months {Tournigand 2004}. The FOLFIRI and FOLFOX6 associations were evaluated for postprogression crossover first-line or second-line treatment. Both arms exhibited similar response rates (first-line treatment: FOLFIRI 56% versus FOLFOX 54% and second-line treatment FOLFIRI 4% versus FOLFOX 15%). There were no significant differences in terms of progression-free survival (PFS) (first-line treatment: FOLFIRI 8.5 months versus FOLFOX 8.0 months and second-line treatment FOLFIRI 2.5 months versus FOLFOX 4.2 months) or of overall survival (OS) (FOLFIRI-FOLFOX: 21.5 months versus FOLFOX-FOLFIRI 20.6 months).

1.3.2. Bevacizumab in Metastatic Colorectal Cancer

Progress in molecular biology has enabled better understanding of the cell signaling process involved in tumors growth and proliferation, subsequently enabling the development of target agents in the treatment of solid tumors. These agents have been devised to interfere with the major processes involved in tumor function. The most promising progress at the present time

involves VEGF inhibition. The VEGF is a strong factor in tumor angiogenesis, permeability, and tumor vascularization survival {Gerber 2005}. The VEGF inhibition induces the destruction of recent neomicrovascularization and endothelial cell apoptosis {Erber 2004, Ferrara 2004}.

One of the most noteworthy VEGF pathway inhibitors is bevacizumab, a humanized monoclonal antibody targeting circulatory VEGF and preventing tumor angiogenesis. The binding of bevacizumab with VEGF prevents the latter from binding with its endothelial cell membrane receptors (Flt-1 and kinase insert domain receptor [KDR]). The interaction of VEGF with its receptors, in angiogenesis models, induces tumor growth and neovessel formation.

Randomized clinical studies have shown that bevacizumab combined with fluoropyrimidine-based chemotherapy is an effective treatment of patients with mCRC, and such combinations are now considered the standard treatment in the first-line and second-line settings {Hurwitz 2004, Saltz 2008, Tebbutt 2010}. Various studies have validated bevacizumab efficacy in patients who had no prior exposure or were treated with bevacizumab. In the bevacizumab-naive second-line setting, longer PFS (7.3 versus 4.7 months, hazard ratio [HR] = 0.61, *P* value < 0.001) and OS (12.9 versus 10.8 months, HR = 0.75, *P* value = 0.0011), as well as a better response rate (22.7% versus 8.6%, *P* value = 0.0001), were observed in the E3200 study comparing the combination of FOLFOX and bevacizumab with FOLFOX alone for patients with CRC who progressed after FOLFOX therapy {Giantonio 2007}.

The ML18147 study {Bennouna 2013} and the BEBYP study {Masi 2012} indicate that continued VEGF inhibition with bevacizumab plus standard second-line chemotherapy (switched over from the first-line regimen) beyond first disease progression significantly prolongs OS and PFS in patients with mCRC. Continuation on bevacizumab for those who progressed after first-line chemotherapy was still helpful for PFS (5.7 versus 4.1 months, HR = 0.68, *P* value < 0.001) and OS (11.2 versus 9.9 months, HR = 0.81, *P* value = 0.0062) improvement compared with standard chemotherapy alone.

1.3.3. Information on Study Auxiliary Medicinal Products/Noninvestigational Medicinal Products

Acetaminophen, diphenhydramine, and corticosteroids are considered auxiliary medicinal products (AxMPs) for this clinical study (Appendix 11). Acetaminophen is approved for pain relief and fever reduction. Diphenhydramine is an antihistamine and is approved for amelioration of allergic reactions. Corticosteroids are anti-inflammatory medications and are used for the amelioration of allergic reactions. The use of acetaminophen, diphenhydramine, and corticosteroids (eg, dexamethasone) on this study is described in Section 5.5.3 “Premedication and Prophylaxis for Magrolimab.” Additional details on acetaminophen, diphenhydramine, and corticosteroids (eg, dexamethasone) can be found in the prescribing information.

1.4. Rationale for This Study

1.4.1. Retreatment/Rechallenge

Due to few efficacious options in later lines, retreatment with a systemic therapy using an earlier line of treatment is common, based on response and toxicity data.

According to the National Comprehensive Cancer Network (NCCN) guidance for patients who had therapy stopped for a reason other than disease progression (eg, use as adjuvant therapy, cumulative toxicity, treatment break, patient preference, etc), rechallenge is an acceptable option.

1.4.2. Therapy Sequencing

Results from a randomized study to evaluate the efficacy of FOLFOX and FOLFIRI regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first progression showed neither sequence to be significantly superior with respect to PFS or OS.

There is a correlation with increase in OS if 5-FU, LV, oxaliplatin, and irinotecan are utilized at some point in the continuum of care, irrespective of order.

1.4.3. Inclusion of Bevacizumab- or anti-EGFR-Experienced Patients

CCI [redacted]

1.4.4. KRAS All-Comers

CCI [redacted]

1.4.5. Combination With Chemotherapy

CCI [redacted]

1.4.6. FOLFIRI as Chemotherapy Backbone

CCI [redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]


CCI

1.4.7. Combination With Bevacizumab

In addition to antiangiogenic properties, targeting the VEGF pathway with bevacizumab has been reported to reduce infiltration of immunosuppressive monocyte-derived suppressor cells and regulatory T cells as well as to upregulate cytotoxic T cells to the tumor microenvironment.

1.4.8. Randomization

A 2:1 randomization allows more patients to access experimental treatment and will increase study participation.

1.5. Rationale for Dose Selection of Magrolimab

CCI

[redacted]

1.6. Risk/Benefit Assessment for the Study

Metastatic colorectal cancer ranks as the second most lethal cancer and the third most prevalent malignant tumor worldwide. Although screening strategies and new treatment modalities have started to reduce the overall CRC death rate, the development of advanced metastatic disease is still associated with poor long-term survival. Recent data has demonstrated a continued decline in incidence and mortality in patients at least 65 years of age but a converse increase among those less than 65 years of age.

Systemic chemotherapy in combination with anti-EGFR antibodies such as cetuximab and panitumumab have significantly improved prognosis in KRAS wild-type patients {Lee 2015}. In addition, patients with MSI-H have demonstrated impressive responses to checkpoint inhibitors such as pembrolizumab {Le 2015, Overman 2016}, but this represents only a subset of this tumor type (10% to 15% at diagnosis). On the other hand, certain subsets of patients such as those with KRAS mutations, which comprise over 40% of CRCs do not respond to anti-EGFR antibody therapies {Allegra 2009}. Patients with KRAS-mutant mCRC have a poorer prognosis while having limited available therapies. For the majority of patients who are ineligible or unable to derive benefit from novel targeted therapies or immunotherapies, SOC doublet or triplet chemotherapy based regimens that are associated with systemic toxicity, unsatisfying response

rates, unpredictable innate and acquired resistance, as well as low tumor-specific selectivity are the only available treatment options. Therefore, significant and clinically relevant improvements in efficacy that advance the treatment landscape are still needed to address this high unmet medical need in patients with CRC.

Magrolimab is a recombinant humanized anti-CD47 monoclonal antibody that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells. Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this MOA and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

CCI [redacted]

CCI [redacted]

An infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 3 for further details on the risks and risk mitigation strategy.

In summary, based on strong scientific rationale, nonclinical, and the lack of substantial anticipated overlapping toxicities with the proposed magrolimab combination regimens, this study has an acceptable risk: benefit ratio for patients who participate.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
Safety Run-in Cohort: • To evaluate the safety, tolerability, and recommended Phase 2 dose (RP2D) of magrolimab in combination with bevacizumab and FOLFIRI in previously treated patients with advanced inoperable mCRC Randomized Cohort: • To evaluate the efficacy of magrolimab in combination with bevacizumab and FOLFIRI in mCRC as determined by PFS by investigator assessment	Safety Run-in Cohort: • Incidence of dose-limiting toxicities (DLTs), adverse events (AEs), and laboratory abnormalities according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Randomized Cohort: • PFS, defined as the time from the date of randomization until the earliest date of documented disease progression as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V1.1), or death from any cause, whichever occurs first
Secondary Objectives	**Secondary Endpoints**
Randomized Cohort: • To evaluate objective response rate (ORR) by investigator assessment • To evaluate additional measures of efficacy of magrolimab in combination with bevacizumab and FOLFIRI, including duration of response (DOR) and OS • To evaluate patient-reported outcomes (PRO)/quality-of-life measures for the Randomized Cohort in mCRC with magrolimab in combination with bevacizumab and FOLFIRI Safety Run-in and Randomized Cohort: • To evaluate the PK and immunogenicity of magrolimab in combination with bevacizumab and FOLFIRI	Randomized Cohort: • Confirmed ORR, defined as the proportion of patients with complete response (CR) or partial response (PR) on 2 consecutive assessments, at least 28 days apart, as determined by investigator assessment using RECIST V1.1 • DOR, defined as time from first documentation of CR or PR to the earliest date of documented disease progression as determined by investigator assessment, per RECIST V1.1, or death from any cause, whichever occurs first • OS, defined as time from date of randomization to death from any cause • PRO assessments (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire [EORTC-QLQ-C30], the 5-level EuroQol 5 dimensions questionnaire [EQ-5D-5L]) scores, and Functional Assessment of Cancer Therapy [FACT] Colorectal Symptom Index [FCSI] Safety Run-in and Randomized Cohorts: • Magrolimab concentration versus time and antidrug antibodies (ADA) to magrolimab
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 2, randomized, open-label, multicenter study to evaluate magrolimab in combination with bevacizumab and FOLFIRI in previously treated patients with advanced inoperable mCRC who have progressed [redacted]

This study will consist of the following 2 cohorts:

- **Safety Run-in Cohort:** magrolimab in combination with bevacizumab and FOLFIRI in previously treated patients with advanced inoperable mCRC

After completion of the Safety Run-in Cohort, the Randomized Cohort will be open to enrollment.

- **Randomized Cohort:** magrolimab in combination with bevacizumab and FOLFIRI (Experimental Arm A) versus bevacizumab and FOLFIRI (Control Arm B) in previously treated patients with advanced inoperable mCRC.

The study schema is presented in Figure 1.

3.1.1. Safety Run-in Cohort

Initially, approximately 6 patients will be enrolled in the Safety Run-in Cohort at a starting dose level. A DLT-assessment period of 28 days will occur (see Section 3.1.1.1).

Although no dose-dependent toxicities have been observed with magrolimab, in order to preserve the efficacious doses of the combination partner drugs, dose de-escalation will take place for magrolimab as follows:

[redacted]

3.1.1.1. Dose-Limiting Toxicity Assessment Period for Safety Run-in Cohort

The DLT-assessment period will be the first 28 days and applies to the Safety Run-in Cohort. Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT-assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- The patient did not experience a DLT and completes at least 3 infusions of magrolimab and at least 2 doses of bevacizumab and FOLFIRI in the Safety Run-in Cohort.

If a patient experiences a DLT during the DLT-assessment period, the patient will discontinue treatment. Patients who are not evaluable for DLT assessment in the Safety Run-in Cohort will be replaced.

Patients enrolled in the Safety Run-in Cohort may continue treatment at the RP2D until unacceptable toxicity, disease progression, or other protocol-specified discontinuation.

3.1.1.2. Dose-Limiting Toxicity Definition for Safety Run-in Cohort

All toxicities will be graded according to the NCI CTCAE, Version 5.0 (Appendix 5).

A DLT is defined as any:

- Grade 3 or higher hematologic toxicity including
  - Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life
  - Grade 4 neutropenia lasting > 7 days, regardless of supporting measures
- An event meeting Hy's Law criteria (Section 7.7).
- Grade 3 or higher nonhematologic toxicity that has worsened in severity from pretreatment baseline during the DLT-assessment period.
- Grade 3 fatigue lasting > 7 days.
- In the opinion of the investigator, the AE is at least possibly related to magrolimab.

The following are exceptions to the DLT definition and are not considered a DLT:

- Grade 3 anemia.
- Grade 3 febrile neutropenia that has responded clinically within 72 hours of maximal supportive care.

- Grade 3 neutropenia that resolves to Grade 2 or pretreatment/baseline with supportive care (including growth factors) within 21 days or Grade 4 neutropenia lasting for 7 days or less with supportive measures.
- Grade 3 thrombocytopenia in the absence of clinically significant bleeding that resolves to Grade 2 or pretreatment/baseline within 3 weeks.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to Grade 2 or lower with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 electrolyte abnormalities that improve to less than or equal to Grade 2 or baseline within 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions.
- Grade 3 elevation in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) up to 8 × upper limit of normal (ULN) lasting less than 7 days. Grade 3 elevation in alkaline phosphatase that resolves to Grade 2 or lower with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 nausea/vomiting or diarrhea that resolves to Grade 2 or lower within 72 hours with adequate antiemetic and other supportive care.
- Grade 3 fatigue that resolves to Grade 2 or lower within 1 week.
- Grade 3 infusion reactions in the absence of an optimal pretreatment regimen, which is defined in Section 5.5.3.
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to less than or equal to Grade 2 or baseline within 72 hours.
- Grade 3 hypomagnesemia that resolves to less than or equal to Grade 2 or baseline within 72 hours.
- Grade 3 or 4 lymphopenia or leukopenia not associated with other clinically significant consequences.
- Transient (≤ 48 hours) Grade 3 local reactions, flu-like symptoms, myalgias, fever, headache, acute pain, or skin toxicity that resolves to Grade 2 or lower within 72 hours after medical management (eg, supportive care, including immunosuppressant treatment) has been initiated.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor, that resolves within 72 hours with supportive care measures.
- Grade 3 lipase and/or amylase elevation without clinical or radiologic evidence of pancreatitis.

3.1.1.2.1. Safety Review Team

A Safety Review Team (SRT) will make dose selection and/or dose modification decisions for individual patients based on data described in Section 3.1.1.

An SRT charter defining the team membership, meeting conduct, and decision-making process will be agreed upon by all team members before the first meeting. The data reviewed at the team meetings to make dose selection and/or dose modification (including dose escalation or dose reduction) decisions will be defined in the charter. The quality control checks performed on the data reviewed and used for making dose selection and/or dose modification decisions will also be described in the charter.

3.1.2. Randomized Cohort

Once the Safety Run-in Cohort is completed and the RP2D for magrolimab in combination with bevacizumab and FOLFIRI is determined, the sponsor will open the Randomized Cohort.

In this open-label, randomized, 2-arm study, patients with mCRC will be randomized in a 2:1 ratio to receive either magrolimab in combination with bevacizumab and FOLFIRI (Experimental Arm A) or bevacizumab and FOLFIRI (Control Arm B).

The primary efficacy assessment will be investigator assessed PFS, with the primary analysis to occur after 85 PFS events. Stratification factors for randomization include the following: (1) KRAS mutation/unknown versus wild-type status, (2) geographic region (US versus EU/rest of world [ROW]), (3) presence versus absence of liver metastases.

3.1.2.1. Treatment-Related Toxicity Monitoring

Treatment-related toxicity will be monitored by a Gilead Data Review Committee (GDRC) at a preset frequency with the stopping boundaries shown in Table 4. The GDRC will convene after CCI patients from Arm A are treated at the dose level for the Randomized Phase 2 Cohort CCI of follow-up, and thereafter when safety data from CCI Arm A patients from CCI become available. The frequency of GDRC review will be outlined in the GDRC charter. This is a Pocock-type boundary {Ivanova 2005} that yields the probability of crossing the boundary of at CCI when the CCI

Table 4. Stopping Boundaries Due to Toxicity (Phase 2 Randomized Cohort Arm A)

	CCI	

TEAE = treatment-emergent adverse event

3.2. Study Treatments

Details regarding the doses and dosing regimens of magrolimab, bevacizumab, and FOLFIRI are provided in Sections 5.5 and 5.6. Details regarding the formulation, packaging, and labeling of magrolimab, bevacizumab, and FOLFIRI are provided in Sections 5.2, 5.3, and 5.4.

3.3. Duration of Treatment

All patients will continue study treatment unless they meet study treatment discontinuation criteria (Section 3.4). Magrolimab can be continued if combination partner drugs (ie, FOLFIRI and/or bevacizumab) are discontinued for unacceptable toxicity. Combination partner drugs can be continued if magrolimab is discontinued for unacceptable toxicity.

CCI [redacted]

3.4. Discontinuation Criteria

3.4.1. Early Discontinuation From Study Treatment

CCI [redacted]

[redacted]

3.4.2. Early Discontinuation From the Study

A patient may permanently discontinue from the study for reasons including but not limited to the following:

- Death
- Pregnancy
- Investigator decision to remove patient from the study
- Protocol violation by the patient
- Patient request, with or without a stated reason
- Patient lost to follow-up
- Study terminated by the sponsor
- Withdrawal of consent

Procedures for patients who discontinue the study early are described in Section 6.4.

3.5. Definitions for Time of Primary Endpoint and End of Study

3.5.1. Primary Endpoint

The date for the last patient's visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.5.2. End of Study

All patients: the end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual patients: patients are considered to have completed study participation altogether when they are no longer followed for survival.

All patients will be followed for survival until death, withdraw from consent, lost to follow-up, and the end of study, whichever occurs first.

For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

3.6. Poststudy Care

After the patient has completed/terminated their participation in the study, long-term care of the patient will remain the responsibility of their primary treating physician.

3.7. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), central laboratory, local laboratory, and/or specialty laboratory (for PK, ADA, and/or PD data) and/or additional biomarker testing, interactive response technology (IRT), imaging, and PRO.

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 135 patients may be enrolled in the study, with approximately 6 to 18 patients in the Safety Run-in Cohort (additional patients could be enrolled in this cohort or in dose de-escalation cohorts) and approximately 117 patients in the Randomized Cohort Arms A and B.

4.1.1. Patient Replacement

Patients may be replaced in the Safety Run-in Cohorts if not evaluable for DLT assessment, as described in Section 3.1.1.

4.2. Inclusion Criteria

All patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Patient has provided informed consent.

2) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.

3) Male or female, at least 18 years of age.

4) Previously treated patients with inoperable mCRC who have progressed on or after 1 prior systemic therapy and who are ineligible for checkpoint inhibitor therapy (eligible patients for checkpoint inhibitor therapy are defined as MSI-H or mismatch repair deficient [dMMR] and are excluded). Note: maintenance therapies are not counted as separate lines of therapy.

5) CCI [redacted]

6) Histologically or cytologically confirmed adenocarcinoma originating in the colon or rectum (excluding appendiceal and anal canal cancers) who have progressed on or after 1 prior systemic therapy in the setting where curative resection is not indicated. This therapy must have included chemotherapy based on 5-FU or capecitabine with oxaliplatin and either bevacizumab, or for patients with RAS wild-type and left-sided tumors, bevacizumab, cetuximab, or panitumumab.

7) Measurable disease (at least 1 measurable metastatic lesion by RECIST V1.1 criteria.CCI [redacted]

8) Patients must have an ECOG performance status of 0 or 1.

9) Life expectancy of at least 12 weeks.

10) Laboratory measurements, blood counts:

a) CCI [redacted]

b) CCI [redacted]

c) Platelets at least 100×10^9/L.

11) Adequate liver function, CCI [redacted]:

CCI [redacted]

[redacted]

[redacted]

12) Patients must have adequate renal function CCI [redacted].

13) Pretreatment blood cross-match completed (see Section 7.8.1.2).

14) CCI [redacted].

15) Criterion removed.

4.3. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Prior anticancer therapy including chemotherapy, hormonal therapy, or investigational agents within 3 weeks or within at least 4 half-lives prior to magrolimab dosing (up to a maximum of 4 weeks), whichever is shorter.

2) Known BRAF V600E or MSI-H mutations or dMMR.

3) Persistent Grade 2 or more gastrointestinal bleeding.

4) CCI [redacted]

5) Patients with prior irinotecan therapy.

6) Criterion removed.

7) CCI [redacted]

8) Clinically significant coronary artery disease or myocardial infarction within 6 months prior to inclusion.

9) Peripheral neuropathy of more than Grade 2 (CTCAE Version 5.0).

10) Known dihydropyrimidine dehydrogenase deficiency.

11) Acute intestinal obstruction or subobstruction, history of inflammatory intestinal disease or extended resection of the small intestine. Presence of a colonic prosthesis.

12) Unhealed wound, active gastric or duodenal ulcer, or bone fracture.

13) History of abdominal fistulas, trachea-oesophageal fistulas, any other Grade 4 gastrointestinal perforations, nongastrointestinal fistulas, or intra-abdominal abscesses 6 months prior to screening.

14) Uncontrolled arterial hypertension CCI [redacted]

15) History of hypertensive crisis or hypertensive encephalopathy.

16) Thromboembolic event in the 6 months before inclusion (eg, transitory ischemic stroke, stroke, subarachnoid hemorrhage) except peripheral deep vein thrombosis treated with anticoagulants.

17) CCI [redacted]

[redacted]

19) Active central nervous system (CNS) disease. Patients with asymptomatic and stable, treated CNS lesions (radiation and/or surgery and/or other CNS-directed therapy who have not received corticosteroids for at least 4 weeks) are allowed.

20) RBC transfusion dependence, defined as requiring more than 2 units of packed RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during the CCI [redacted].

21) History of hemolytic anemia, autoimmune thrombocytopenia, or Evans syndrome in the last 3 months.

22) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.

23) CCI [redacted]

[redacted]

25) Known inherited or acquired bleeding disorders.

26) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. CCI [redacted]

27) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, CCI [redacted].

28) Known active or chronic hepatitis B or C infection. Hepatitis B or C patients not currently on antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study. Patients with serologic evidence of prior vaccination to hepatitis B virus (ie, hepatitis B surface antigen negative and antibody against hepatitis B surface antigen positive) may participate.

29) Uncontrolled pleural effusion.

30) CCI [redacted]

[redacted].

32) Severe/serious systemic infection within 4 weeks of randomization or any active, uncontrolled infection requiring systemic therapy within 7 days of randomization.

33) Presence of a detectable HIV viral load in patients with a known history of HIV.

CCI [redacted]

5. STUDY DRUGS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Patients who are eligible for the Randomized Cohort will be randomized in a 2:1 ratio to receive either magrolimab + bevacizumab + FOLFIRI or bevacizumab + FOLFIRI starting on the Day 1 visit and assigned a patient number.

CCI [redacted]

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this open-label study.

5.2. Description and Handling of Magrolimab

5.2.1. Formulation

CCI [redacted]

5.2.2. Packaging and Labeling

CCI [redacted]

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guidelines to Good Manufacturing Practice, Annex 6 for Clinical Trials Regulation (CTR), and/or other local regulations.

5.2.3. Storage and Handling

Magrolimab should be stored at CCI [redacted] Do not shake. Storage conditions are specified on the label. Refer to the Pharmacy Manual for instructions on reporting temperature excursions. Until dispensed to the patients, study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Bevacizumab

5.3.1. Formulation

Information regarding the formulation of bevacizumab can be found in the local prescribing information.

The use of an approved biosimilar is permitted upon approval by the sponsor.

5.3.2. Packaging and Labeling

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Annex 6 for CTR, and/or other local regulations. Alternatively, in alignment with local regulations commercial product may be sourced locally by the sites.

5.3.3. Storage and Handling

Further information regarding storage and handling of bevacizumab is available in the local prescribing information.

5.4. Description and Handling of FOLFIRI

5.4.1. Formulation

Information regarding the formulation of FOLFIRI (irinotecan, LV, and 5-FU) can be found in the local prescribing information for each agent {CAMPTOSAR 2020, FLUOROURACIL 2016, LEUCOVORIN 2011, LEVOLEUCOVORIN 2016}.

5.4.2. Packaging and Labeling

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Annex 6 for CTR, and/or other local regulations. Alternatively, in alignment with local regulations commercial product may be sourced locally by the sites.

5.4.3. Storage and Handling

Further information regarding storage and handling of FOLFIRI (irinotecan, LV, and 5-FU) is available in the local prescribing information for each agent {CAMPTOSAR 2020, FLUOROURACIL 2016, LEUCOVORIN 2011, LEVOLEUCOVORIN 2016}.

Study treatments for the Safety Run-in Cohort and the Randomized Cohort are summarized in Table 5 and Table 6, respectively.

5.5. Dosage and Administration of Magrolimab

The magrolimab dosing regimen for the safety run-in and randomized cohorts is presented in Table 5 and Table 6. Treatment administration and associated assessment schedules for magrolimab repriming are provided in Appendix Table 1.

Table 5. Safety Run-in Cohort Dosing and Dose De-escalation Regimen

Drug/Dose/Route	Dose Schedule (Day per 28-Day Cycle)		
	Cycle 1	Cycle 2	Cycle 3+
Bevacizumab 5 mg/kg IV every 2 weeks[a]	Days 1, 15	Days 1, 15	Days 1, 15
FOLFIRI IV[b] Irinotecan 180 mg/m^2 over 30-90 minutes on first day of dose administration Leucovorin 400 mg/m^2 over 2 hours on first day of dose administration[c] Fluorouracil 400 mg/m^2 bolus on first day of dose administration, followed by 2400 mg/m^2 over 46 hours, continuous infusion	Days 1, 15	Days 1, 15	Days 1, 15
Magrolimab Administration			
Magrolimab 1 mg/kg IV (3 hours ± 30 min)	Day 1		
Magrolimab starting dose level 30 mg/kg IV (2 hours ± 30 min)	QW beginning at Day 8 visit and the next 6 doses (Cycle 1 Days 8, 15, and 22, Cycle 2 Days 1, 8, 15, and 22)		
Magrolimab 30 mg/kg IV (2 hours ± 30 min)	Q2W beginning 1 week after the last weekly 30 mg/kg dose (starting Cycle 3 Day 1 onward)		
Magrolimab de-escalation Level −1 20 mg/kg IV (2 hours ± 30 min)	QW beginning at Day 8 visit and the next 6 doses (Cycle 1 Days 8, 15, and 22, Cycle 2 Days 1, 8, 15, and 22) Q2W beginning 1 week after the last weekly 20 mg/kg dose (starting Cycle 3 Day 1 onward)		
Magrolimab de-escalation Level −2 15 mg/kg IV (2 hours ± 30 min)	QW beginning at Day 8 and the next 6 doses (Cycle 1 Days 8, 15, and 22, Cycle 2 Days 1, 8, 15, and 22) Q2W beginning 1 week after the last weekly 15 mg/kg dose (starting Cycle 3 Day 1 onward)		

FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; IV = intravenous; QW = every week; Q2W = every 2 weeks

a Bevacizumab should be administered per standard of care and/or institutional guidelines. CCI [redacted]

b FOLFIRI should be administered per standard of care and/or institutional guidelines. Recommendations include administering the first dose of irinotecan over 30-90 minutes CCI [redacted]

c Levoleucovorin 200 mg/m^2 may be used if leucovorin is unavailable. Generics for leucovorin or levoleucovorin are also permitted. Leucovorin and levoleucovorin should be administered per standard of care and/or institutional guidelines. Recommendations include administering the first dose over 2 hours. Different leucovorin doses may be used if recommended by regional or institutional guidelines.

Table 6. Randomized Cohort Dosing Regimen

Drug/Dose/Route	Dose Schedule (Day per 28-Day Cycle)		
	Cycle 1	**Cycle 2**	**Cycle 3+**
Bevacizumab 5 mg/kg IV every 2 weeks[a]	Days 1, 15	Days 1, 15	Days 1, 15
FOLFIRI IV[b] Irinotecan 180 mg/m^2 over 30-90 minutes on first day of dose administration Leucovorin 400 mg/m^2 over 2 hours on first day of dose administration[c] Fluorouracil 400 mg/m^2 bolus on first day of dose administration, followed by 2400 mg/m^2 over 46 hours, continuous infusion	Days 1, 15	Days 1, 15	Days 1, 15
Magrolimab Administration			
Magrolimab 1 mg/kg IV (3 hours ± 30 min)	Day 1		
Magrolimab RP2D IV (2 hours ± 30 min)	QW beginning at Day 8 visit and the next 6 doses (Cycle 1 Days 8, 15, and 22, Cycle 2 Days 1, 8, 15, and 22)		
Magrolimab RP2D IV (2 hours ± 30 min)	Q2W beginning 1 week after the last weekly RP2D (starting Cycle 3 Day 1 onward)		

FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; IV = intravenous; QW = every week; Q2W = every 2 weeks;
CCI

a Bevacizumab should be administered per standard of care and/or institutional guidelines. CCI

b FOLFIRI should be administered per standard of care and/or institutional guidelines. Recommendations include administering the first dose of irinotecan over 30-90 minutes. CCI

c Levoleucovorin 200 mg/m^2 may be used if leucovorin is unavailable. Generics for leucovorin or levoleucovorin are also permitted. Leucovorin and levoleucovorin should be administered per standard of care and/or institutional guidelines. Recommendations include administering the first dose over 2 hours. Different leucovorin doses may be used if recommended by regional or institutional guidelines.

CCI

CCI

[redacted]

CCI [redacted]

Table 7. Repriming Guidelines for Magrolimab

Dose	Dosing Frequency	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	NA – used at initial priming	2 weeks
15 mg/kg	Weekly or more frequent (Cycle 1 Days 8, 15, 22, Cycle 2 Days 1, 8, 15, 22)	2 weeks
	Every 2 weeks (from Cycle 3 Day 1)	4 weeks
20 mg/kg	Weekly or more frequent (Cycle 1 Days 8, 15, 22; Cycle 2 Days 1, 8, 15, 22)	2 weeks
	Every 2 weeks (from Cycle 3 Day 1)	4 weeks
30 mg/kg	Weekly or more frequent (Cycle 1 Days 8, 15, 22; Cycle 2 Days 1, 8, 15, 22)	2 weeks
30 mg/kg	Every 2 weeks (from Cycle 3 Day 1)	4 weeks

NA = not applicable

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

5.6. Dosage and Administration of Bevacizumab and FOLFIRI

The bevacizumab and FOLFIRI dosing regimen for the safety run-in and randomized cohorts is presented in Table 5 and Table 6.

CCI [redacted]

5.7. Prior and Concomitant Medications

5.7.1. Permitted Concomitant Medications for All Cohorts

For the regimens administered with magrolimab in this study, the current local or regional prescribing information should be consulted regarding permitted and prohibited concomitant medications.

Premedication, as well as prophylaxis for AEs as described in Section 5.5.3, are permitted while on study treatment.

CCI [redacted]

All concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received after informed consent through the study treatment period, through the 30-day safety follow-up visit should be recorded in the eCRF.

5.7.2. Coronavirus Disease 2019 (COVID-19) Vaccine

There is no contraindication to the COVID-19 vaccine with magrolimab. There is no specific recommendation on the timing of a COVID-19 vaccine; individuals may receive the vaccine when available. However, if these patients are neutropenic, investigators may use local guidance as well as clinical judgment in determining the timing of the COVID-19 vaccine. Investigators should document vaccinations. Investigators should notify patients of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection.

5.7.3. Prohibited Concomitant Medications

Anticancer therapies including chemotherapy, targeted therapies, and immunotherapy (apart from study drugs) are not permitted while patients are on study.

5.8. Accountability for Study Drug(s)

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (kits, vials, etc). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug (kits, vials, etc) dispensed to patients must be returned to the site.

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug (kits, vials, etc)
- The date, patient number, and the study drug (kits, vials, etc) number dispensed
- The date, quantity of used and unused study drug (kits, vials, etc) returned, along with the initials of the person recording the information

5.8.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient screened or enrolled in the study are presented in tabular form in Table 1, Table 2, and Table 3 and are described in the sections below.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Informed Consent

Written informed consent must be obtained from each patient before initiation of any study-related procedures. Refer to Section 9.1.4 for further information regarding informed consent.

6.1.1. Informed Consent for Optional Research

In addition to the study-specific informed consent form to be signed by each patient participating in the study, patients will be required to document additional consent to provide the following, in accordance with applicable regulations:

- CCI [redacted]

6.2. Prescreening, Screening, Patient Enrollment, and Treatment Assignment

An IRT system will be employed to manage the conduct of the study. The IRT will be used to maintain a central log documenting enrollment, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study drug.

Patients will be screened within 30 days before enrollment/randomization in the study. CCI [redacted] Each patient will be assigned a unique screening number using the IRT. Patients meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days for enrollment/randomization into the study starting on Cycle 1 Day 1 and assigned a patient number and treatment arm by the IRT. Rescreening will be permitted. Assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period.

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.2.1. Prescreening

Prior to providing consent for the study, an optional prescreening consent form may be offered to patients at the investigator's discretion to permit the collection and analysis of CCI [redacted]

6.3. Instructions for Study Procedures

Study procedures and assessments are outlined in Table 1, Table 2, and Table 3.

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record serious adverse events (SAEs) that are considered related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs. Additional details are provided in Section 7.

6.3.2. Type and Screen and Direct Antiglobulin Test

Please refer to Section 7.8.1.1 for detailed guidance on type and screen and DAT.

6.3.3. Concomitant Medications

Review of concomitant medications will occur at the time points presented in Table 1, Table 2, and Table 3.

All concomitant medications taken by the patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after informed consent through the study treatment period, and until 30-day safety follow-up visit. Concomitant medication associated with procedure-related AEs will be captured from the time of informed consent and onward. Information to be collected includes drug name, indication, route, start date, and stop date, and must be reported using the applicable eCRF. Note that any anticancer therapies after the study treatment period should also be collected per the schedule of assessments.

6.3.4. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential (see Appendix 4 for definition of childbearing potential). Pregnancy tests are performed as specified in the schedule of assessments (Table 1, Table 2, and Table 3).

6.3.5. Physical Examination

Complete physical examination should be performed at screening. Symptom-directed physical are performed from Day 1.

6.3.6. Vital Signs, Weight, and Height

Vital signs should include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height should be recorded during screening only. Weight should be recorded during screening and every 4 weeks thereafter. Vital signs are to be recorded prior to dosing of study treatment at the visits specified in the schedule of assessments (Table 1, Table 2, and Table 3). Vital signs will be collected postdose (as clinically appropriate).

6.3.7. Electrocardiograms

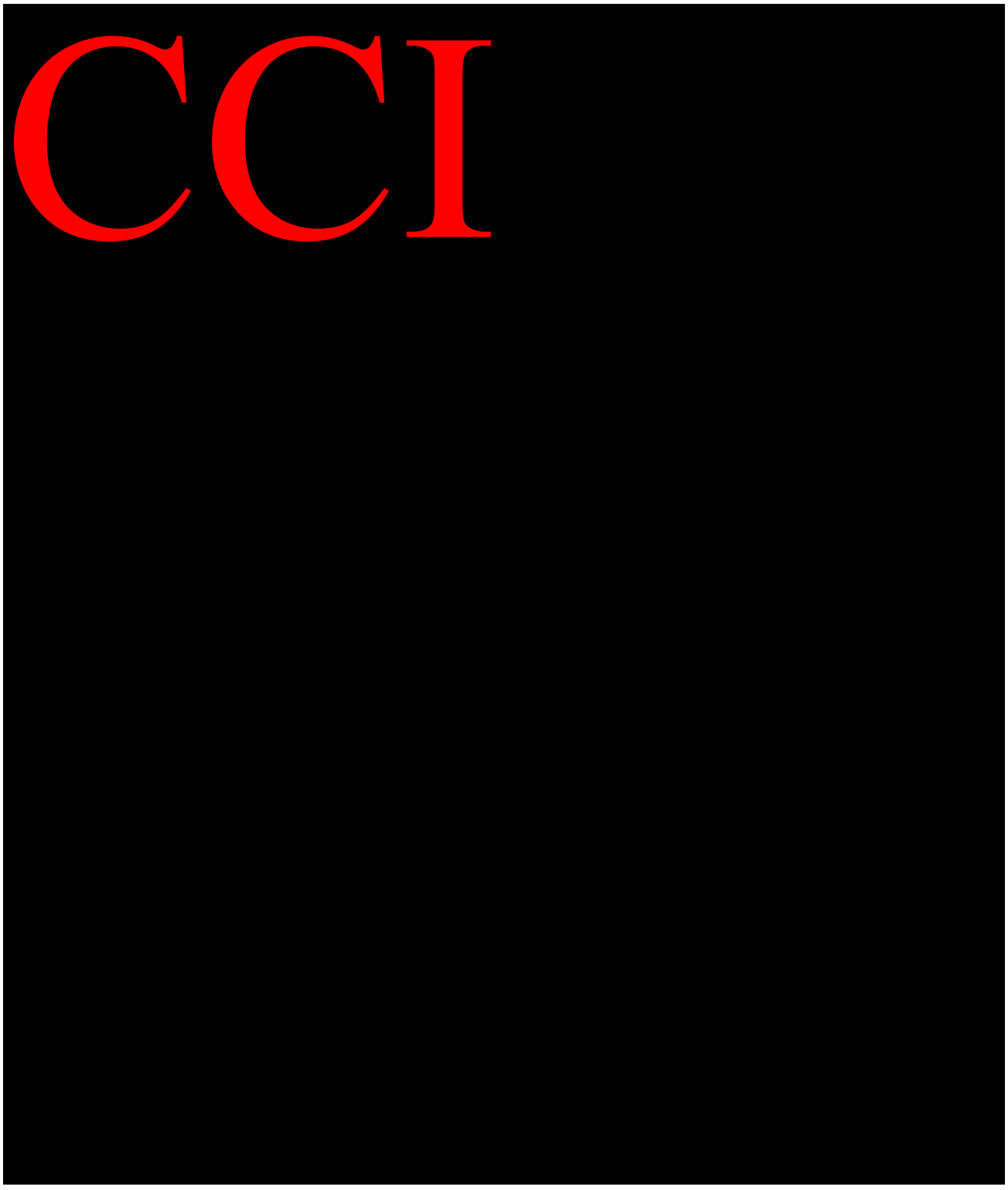
A single electrocardiogram (ECG) will be performed at screening.

6.3.8. Performance Status

Performance status will be scored using the ECOG performance status scale index (refer to Appendix 6).

6.3.9. Clinical Laboratory Assessments

CCI [redacted]


CCI

6.3.10. Efficacy Assessments

CCI [redacted]

Appropriate cancer staging assessments should be performed. Imaging assessments are to be conducted according to the RECIST V1.1 criteria for solid tumors {Eisenhauer 2009}. The same imaging modality used at screening should be used throughout the study whenever possible. It is understood that some circumstances may require a different imaging modality. An alternate imaging modality is acceptable and may be performed at the investigator's discretion.

Per RECIST criteria, if a patient achieves an initial objective response (CR/PR) on imaging, an imaging assessment at least 4 weeks later is required to confirm the response.

6.3.11. Pharmacokinetics

Magrolimab serum concentration will be measured by a validated enzyme-linked immunosorbent assay immunoassay method.

Blood samples for PK assessment will be collected at predose at multiple time points from patients who received magrolimab according to the schedule of assessments in Table 2 (note the additional sample collected postdose on Cycle 3 Day 1 at 1 hour [± 15 minutes] after the end of magrolimab infusion). Residual samples used for PK and ADA analysis may also be used for exploratory PK or PD analyses related to magrolimab treatment alone as well as combination therapy with anticancer chemotherapies. This could include using leftover serum for exploratory, alternative PK assay development and analysis.

6.3.12. Immunogenicity

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described in the schedule of assessments for patients who are assigned to receive magrolimab (Table 2 and Table 3). When collected on the day of study drug dosing, the blood sample for assessing ADA must be collected at the same time as the predose PK sample. The presence of ADA will be determined by a validated chemiluminescence immunoassay method.

6.3.13. Biomarker Testing

CCI [redacted]

CCI

[redacted]

[redacted]

6.3.14. Patient-Reported Outcomes

For the Randomized Cohort, 3 PRO instruments will be administered in this study: EORTC-QLQ-C30, EQ-5D-5L, and the FCSI. The patient should complete these questionnaires before any other study procedures conducted the same day at required visits. Please refer to Table 2 for timings of PRO assessments. If the PRO questionnaires are unavailable in a patient's language, completion is not required. Patients with other barriers to questionnaire completion may be exempt from these assessments after discussion with the sponsor.

6.3.14.1. EORTC-QLQ-C30

The EORTC-QLQ-C30 is a reliable and valid measure of PROs and has been widely used among patients with cancer (Appendix 8). The EORTC-QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) {Fayers 2001}. The recall period is 1 week (past week). It will take about 11 minutes to complete.

6.3.14.2. EQ-5D-5L

The EQ-5D-5L is an instrument for use as a measure of health outcome {EuroQol Research Foundation 2017}. The EQ-5D-5L consists of 2 sections: the EuroQol (5 dimensions) (EQ-5D) descriptive system and the EuroQol visual analogue scale (EQ-VAS). A sample is provided in Appendix 9.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ-VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labeled "the best health you can imagine" and "the worst health you can imagine."

The EQ-VAS can used as a quantitative measure of health outcome that reflects the patient's own judgment.

6.3.14.3. FACT Colorectal Symptom Index

The FCSI is a well-validated PRO instrument as a set of brief, clinically relevant, colorectal cancer symptoms for assessing symptomatic response. It comprises the most important symptoms associated with colorectal cancer, including energy, pain, weight, diarrhea, nausea, swelling or cramps in the stomach area, appetite, ability to enjoy life, and overall quality of life. Its minimum important difference (MID) range from 1.5 to 3 has been published {Colwell 2010}.

The FCSI questionnaire is provided in Appendix 10.

6.4. Assessments for Early Discontinuation From Study Treatment or From the Study

If a patient discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures (see Section 3.4). If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study.

6.4.1. Assessments for Early Discontinuation From Study Treatment

A patient who discontinues study drug early will be asked to return to the investigational site within 7 days of stopping study drug to attend an early study drug discontinuation visit for assessments and procedures specified in Table 3.

6.5. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for disease progression (if applicable), survival, and AEs. Poststudy treatment assessments are described in Table 3.

6.6. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period CCI or per country requirements. Samples will be stored in compliance with all applicable regulations. CCI

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.1.3).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation. (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization.

- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: such 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 constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

Given progression of disease is one of the endpoints of the study, in order to maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered AEs/SAEs:

- Progression of disease
- Deaths related to progression of disease

Events that are considered to represent progression of disease should not be recorded as AEs/SAEs unless it is assessed that study drugs contributed to disease progression. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE.

Death that is attributed by the investigator as solely due to disease progression and that occurs during the protocol-specified AE reporting period should be recorded only on the death eCRF (ie, not collected as an SAE on the AE eCRF).

7.1.2.1.1. Deaths Not Related to Disease Progression

All other deaths (ie, deaths that are not due to disease progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the AE eCRF and reported within 24 hours of awareness and no later than the next business day.

When recording a death on the eCRF, the event or condition that is considered the primary cause of death should be the AE term, and the outcome should be death. A patient can only have 1 AE (SAE) with outcome of death and severity of Grade 5 (CTCAE Version 5).

7.1.3. Study Drugs and Gilead Concomitant Medications Special Situations Reports

Special situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy, regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE (which includes situations of missed dose), medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a patient.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the patient has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/alcohol interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs/NIMPs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each study drug and noninvestigational medicinal product (NIMP)/AxMP using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting. If the investigator feels that it is reasonably possible that one of the NIMPs/AxMPs caused an event, the attribution will be reported using the alternative causality section of the SAE report in the electronic data capture (EDC).

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE Toxicity Grading Scale, Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 5).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

After informed consent but before initiation of study drug, only SAEs related to protocol-mandated procedures are to be reported, using the applicable eCRFs.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report the AEs on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the initiation of the first dose of study drug and throughout the duration of the study, including the safety follow-up visit, must be reported on the applicable eCRFs and to Gilead Patient Safety (PS) as instructed below in this section. Only SAEs that are considered related to study procedures are to be reported during the screening period.

Any SAEs and deaths that occur within 30 days of the last dose of study drug (safety follow-up visit), regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

The SSRs involving a Gilead concomitant medication (not considered study drug), that occur after the patient first consents to participate in the study (ie, signing of the informed consent form) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.1).

7.3.5.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs because of a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE eCRF. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal patient identification, maintaining the traceability of a document to the patient identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PS within 24 hours of the investigator's knowledge of the event from the time of the informed consent form signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours to:

Gilead PS: Email: PPD
or
Fax: PPD

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

All special situations will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead PS: Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper SSR form and transmitted to:

Gilead PS: Email: PPD
or
Fax: PPD

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs because of a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female patients that are identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period, to Gilead PS within 24 hours of becoming aware of the pregnancy using the pregnancy report form. Contact details for transmitting the pregnancy report form are as follows:

Gilead PS: Email: PPD
or
Fax: PPD

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion because of complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to Gilead PS.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: PPD and fax: PPD.

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA CFR, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant suspected unexpected serious adverse reaction reports associated with any study drug. The investigator should notify the IRB or IEC of suspected unexpected serious adverse reaction reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased Hb).

Severity should be recorded and graded according to the CTCAE Toxicity Grading Scale, Version 5.0 (Appendix 5). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all patients.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment if the investigator determines that it is not in the patient's best interest to continue. Discontinuation of treatment should be considered if there is an indication of severe liver injury according to Hy's Law, defined by FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health and Human Services 2009}, as:

- Treatment-emergent ALT or AST elevation (≥ 3 × ULN), and
- Treatment-emergent total bilirubin elevation (> 2 × ULN), and absence of cholestasis (defined as alkaline phosphatase < 2 × ULN), and
- No other good explanation for the injury (hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure, worsening liver metastases, hemolysis).

7.8. Toxicity Management

7.8.1. Magrolimab

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

7.8.2. Bevacizumab, 5-fluorouracil, Irinotecan, and Leucovorin/Levoleucovorin

Refer to bevacizumab, 5-FU, irinotecan, LV, and levoleucovorin local prescribing information (eg, summary of product characteristics, US prescribing information) and local guidelines for safety management.

8. STATISTICAL CONSIDERATIONS

Additional details for the planned analyses will be provided in the statistical analysis plan (SAP) including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

The objectives and endpoints are provided in Section 2.

8.2. Planned Analyses

8.2.1. Dose Determination Analysis

For the purpose of making the dose de-escalation decisions the Safety Run-in Cohort, dose determination analyses of relevant safety data focusing on DLTs and overall safety profile will be conducted by the sponsor after all patients have completed the required DLT-assessment period as specified in Section 3.1.1. Safety assessments (eg, AEs, ECG, laboratory test results) will be displayed by cohort to facilitate the dose de-escalation decisions.

8.2.2. Primary Analysis

For the primary analysis, outstanding data queries will have been resolved or adjudicated as unresolvable, and the data will have been cleaned and finalized for the analysis. CCI [redacted]

8.2.3. Final Analysis

The final analysis will be performed after all patients have completed the study or discontinued early, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

8.3.1.1.1. Safety Run-in Cohort

For the Safety Run-in Cohort, the primary analysis set for efficacy analysis is the modified Intent-to-Treat (ITT) Analysis Set, defined as all patients who received at least 1 dose of any study drug.

8.3.1.1.2. Randomized Cohort

For the Randomized Cohort, the primary analysis set for efficacy analysis is the ITT Analysis Set, defined as all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified.

8.3.1.2. Safety

8.3.1.2.1. DLT-Evaluable Analysis Set

For the Safety Run-in Cohort, the primary analysis set for the DLT analysis is the DLT-Evaluable Analysis Set, defined as all patients who meet one of the following criteria in the DLT-evaluable period (defined as the first 28 days):

- Patient experienced a DLT at any time after initiation of the first infusion of magrolimab.
- Patient did not experience a DLT and completes at least 3 infusions of magrolimab and at least 2 doses of bevacizumab and FOLFIRI in the Safety Run-in Cohort.

8.3.1.2.2. Safety Run-in Cohort

For the Safety Run-in Cohort, the primary analysis set for safety analysis, except for DLTs, is the Safety Analysis Set, defined as all patients who received at least 1 dose of any study drug.

8.3.1.2.3. Randomized Cohort

For the Randomized Cohort, the primary analysis set for safety analyses is the Safety Analysis Set, defined as all randomized patients who received at least 1 dose of any study drug, with treatment assignment designated according to the actual treatment received.

8.3.1.3. Pharmacokinetics

The PK analysis will be conducted on the PK Analysis Set, defined as all patients who received any amount of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.3.1.4. Immunogenicity

The immunogenicity analysis will be conducted on the Immunogenicity Analysis Set, defined as all patients who received any amount of magrolimab and have at least 1 evaluable ADA test result.

8.3.1.5. Biomarkers

The biomarker analysis will be conducted on the Biomarker Analysis Set, defined as all patients who received any study drug and have at least 1 evaluable biomarker measurement available.

8.3.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, SD, 95% CIs on the mean, median, minimum, and maximum.

Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by treatment arm.

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study treatment. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of nonnormality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of body weight, height, body mass index, selected laboratory data, medical and cancer history, prior treatment and number of prior treatment(s), tumor imaging for baseline response assessment, randomization stratification group, and ECOG performance status.

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Endpoint Analysis

8.5.1.1. Randomized Cohort

For the Randomized Cohort, PFS by investigator assessment will be analyzed using KM methods. Patients who did not have documented disease progression or death will be censored at the date of their last response assessment during the study with documentation of no disease progression. The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided along with the corresponding 95% CI. A log-rank test stratified by the randomization factors will be used to compare treatment difference in PFS. A stratified Cox proportional hazard regression model will be used to estimate the HR and its 2-sided 95% CI.

CCI [redacted]

8.5.2. Secondary Efficacy Endpoint Analyses

Analysis of OS and DOR will be similar to that of the primary endpoint analysis of PFS for the Randomized Cohort.

Confirmed ORR by investigator assessment will be summarized by count and percentage of patients. A Cochran-Mantel-Haenszel (CMH) chi-square test for association between treatment and response, after adjusting for stratification factors, will be performed to compare the 2 treatment arms. Patients who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders. Odds ratios and corresponding 95% CIs will also be presented.

8.6. Safety Analysis

8.6.1. Primary Safety Endpoint Analysis

For the Safety Run-in Cohort, the incidence of DLTs, AEs, and laboratory abnormalities during the DLT-assessment period by count and percentage will be reported using the DLT-Evaluable Analysis Set. The DLT-assessment period is defined as the first 28 days of dosing.

8.6.2. Other Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days or the day before initiation of subsequent anticancer therapy, whichever comes first, will be summarized by treatment arm (according to the study drug received). Data for the pretreatment and treatment-free safety follow-up periods will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, counts and percentages of patients will be summarized. For continuous safety data, including laboratory data, number of patients, mean, SD, minimum, quartiles, median, and maximum will be summarized.

8.6.3. Extent of Exposure

Data regarding a patient's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by treatment arm.

8.6.4. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the MedDRA. System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study treatment plus 30 days or the day before initiation of subsequent anticancer therapy, whichever comes first.

Summaries (number and percentage of patients) of treatment-emergent AEs (by system organ class, and preferred term) will be provided by treatment arm.

8.6.5. Laboratory Evaluations

Selected laboratory test data (using conventional units) will be summarized using only observed data.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade after the date of first dose of study drug up to the date of last dose of study treatment plus 30 days or the day before initiation of subsequent anticancer therapy, whichever comes first, will be summarized by treatment arm. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the patient has been discontinued from treatment for at least 30 days will be included in a data listing.

8.6.6. Other Safety Evaluations

Vital signs and physical examination findings will be summarized by treatment arm. Details will be provided in the SAP.

8.7. Pharmacokinetic Analysis

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Serum concentrations will be listed and summarized for magrolimab using descriptive statistics by sampling time point and dose level. Graphical plots of individual serum concentration versus time and mean concentration versus time by dose level will be generated. All data from this study may be combined with PK data from other company sponsored clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

8.8. Immunogenicity Analysis

Immunogenicity will be assessed using a 3-tier (screen, confirmatory, and titer) approach on serum samples. The rate of ADA incidence and prevalence will be summarized for the Immunogenicity Analysis Set. Titer and neutralizing antibodies will be determined and reported for ADA positive samples only. Titer data will be listed and neutralizing antibodies will be tabulated by visit and dose level. Exploratory evaluations may be conducted to determine the relationship between ADA positivity and safety, PK, or efficacy parameters (eg, drug concentrations, AEs, disease response) using graphical, tabular, and population PK approaches.

8.9. Biomarker Analysis

The baseline level, absolute level, and change from baseline level over time will be summarized using descriptive statistics for each biomarker at sample collection time point by treatment arm, as appropriate. CCI [redacted].

8.10. Analysis of Patient-Reported Outcome Data

Summary statistics and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC-QLQ-C30, EQ-5D-5L, and FCSI questionnaires at each time point. In addition, mean scores for global health status, physical functioning, and selected symptom scales will be presented. The scores will be derived according to the scoring manual guidelines. The MID-based response rate, time to response, DOR, and time to deterioration will be analyzed like the efficacy endpoints.

8.11. Sample Size

CCI [redacted]

8.12. Gilead Data Review Committee

An internal GDRC will be established to monitor the safety of patients in Randomized Cohort Arm A. The GDRC will perform interim reviews of safety data and assess any treatment-related toxicities per the prespecified stopping rules described in Section 3.1.2.1. The GDRC's specific activities as well as the GDRC's membership, conduct, and meeting schedule will be defined in the GDRC charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last patient completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved informed consent form for documenting written informed consent. Each informed consent form (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The informed consent form will inform patients about genomic testing and/or planned sample retention. In addition to the study-specific informed consent form to be signed by each patient participating in the study, patients will be required to document additional consent to provide additional samples and/or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. The results of the tests performed on the samples will not be given to the patient or the investigator. The stored biological samples will be destroyed no later than 15 years after the end of study or per country requirements, but patients may at any time request that their stored samples be destroyed.

9.1.5. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. Note: the investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remains the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, the informed consent form(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each patient:

- Patient identification
- Documentation that the patient meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])

- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-EDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines

provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [European Commission] No. 1901/2006) after the global end of study (as defined in Section 3.5.2).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study personnel may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any patient records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the case report form/eCRF form at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the patients, appropriate regulatory authority(ies), and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

A Phase 2, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination With Bevacizumab and FOLFIRI Versus Bevacizumab and FOLFIRI in Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)

GS-US-587-6156, Amendment 5, 31 October 2023

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Magrolimab Repriming Administration and Associated Assessment Schedule

Appendix Table 1. Magrolimab Repriming Administration and Associated Assessment Schedule

	[redacted]
Visit Window (Days)[a]	
Cycle Day[b]	
Safety	
CBC with differential, platelets, reticulocytes[c, d]	
[redacted]	
Chemistry[c]	
Vital signs and weight[e]	
Symptom-directed physical examination[c]	
Pregnancy test[f]	
Adverse events[g]	
Concomitant medications[g]	
Magrolimab Administration	
Premedication[h]	
Magrolimab[i]	

CBC = complete blood count; [redacted] WBC = white blood cell

a Any other visit window specifications for individual assessments should be applied.

[redacted]

h Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment in case of reintroduction with repriming. Premedication after the first 4 doses may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent doses is required (Section 5.5.3).

i Magrolimab should not be given on consecutive days. The duration of infusion including flush will be 3 hours (± 30 minutes) for the first dose of magrolimab, and then 2 hours (± 30 minutes) for subsequent infusions. Monitor patients for 1 hour postinfusion, during first 4 weeks for repriming. For magrolimab dosing, please refer to Table 6. If repriming occurs at Cycle 3 onwards, Q2W dosing will begin at this time point.

Appendix 3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study.

These potential risks and mitigation plans can be summarized as follows:

1) Schedule of assessments:

   a) Physical examination:

      i) In order to limit a patient's time in the clinic, a virtual visit may be conducted for the physical examination assessment. Vital signs may be omitted for virtual visits. However, dosing and biological sample collection should occur per protocol in the clinic.

   b) Dosing:

      i) Patients may be unable to return to the site for a number of visits to receive the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

      Mitigation plan: If permitted by local ethics committee/institutional review boards noninvestigational product as determined by sponsor (ie, docetaxel) can be administered at a clinic closer to the patient, under the supervision of a licensed physician. If necessary, a dosing delay for magrolimab must be discussed with the sponsor in this instance. A virtual study visit, via phone or video conferencing, must be performed prior to remote dosing. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be considered to ship the drug from sites to the alternate clinic.

   c) General patient selection guidance:

      i) To minimize patients receiving red blood cell transfusions, we recommend selecting patients with higher hemoglobin thresholds at baseline and use intravenous iron and/or erythropoietin where clinically indicated.

2) Study drug supplies to patients and sites:

   a) Shipments of study drug from the sponsor to the investigational site could be delayed because of transportation issues. Without study drug, the patient would not be able to stay on the study drug as planned per protocol.

      Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

3) Patient safety monitoring and follow-up:

a) Patients may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For patients who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the patient within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if patient has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs

ii) Review current list of concomitant medications and document any new concomitant medications

iii) If applicable, confirm that patient-reported outcomes have been completed and transmitted where possible

b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence, samples may not be analyzed at the site laboratory and/or sent for central laboratory analyses.

Mitigation plan: Accredited local laboratories that are not affiliated with the site may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Alternative sample handling and storage may be possible for samples routinely sent to the central laboratory, sites should refer to the study laboratory manual and discuss with the sponsor for further guidance.

c) Patients may be unable or unwilling to attend the study visit to sign an updated informed consent form version if there is an update.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local independent ethics committee (IEC)/institutional review board (IRB) and national laws and regulations. Remote consent will be allowed if it has been approved by the local IEC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) The safety of study patients is important and testing of coronavirus disease 2019 (COVID-19) infection will be based on local clinical guidelines for testing based on signs/symptoms and or suspected exposure to COVID-19.

Mitigation plan: If patient has a diagnosis of COVID-19 while on this clinical study, study drugs may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general magrolimab dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in the clinical study will have this event documented as an AE in the clinical database.

4) Protocol and monitoring compliance:

   a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form and described in the CSR. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Monitors may be unable to carry out source data review, source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or under reporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on site must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

   a) There may be an increased amount of missing data due to patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternative methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of magrolimab in study patients remains unchanged. In case of an increase in these potential risks, which cannot be mitigated due to the escalation of a pandemic, enrollment of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, women younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b. Definition of Male Fertility

For the purposes of this study, a male-born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Patients

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in an embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated pharmacokinetic interaction with progestin or other steroids based on the distinct clearance pathways.

Bevacizumab is contraindicated in pregnancy as it is anticipated to inhibit angiogenesis in the fetus, and thus is suspected to cause serious birth defects when administered during pregnancy. Advise women of the potential risk to a fetus. No contraindication to hormonal contraception is described in the bevacizumab prescribing information.

FOLFIRI is a therapeutic regimen consisting of 5-fluorouracil (5-FU), irinotecan, and leucovorin. Based on the mechanism of action, 5-FU can cause fetal harm when administered to a pregnant woman. In animal studies, administration of 5-FU at doses lower than a human dose caused teratogenicity. Based on the mechanism of action, irinotecan can cause fetal harm when administered to a pregnant woman. In animal studies, irinotecan has been shown to be

embryotoxic and teratogenic. The patient should be apprised of the potential hazard to a fetus. No contraindication to hormonal contraception is described in the prescribing information of any of the components of FOLFIRI.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within 3 days before study treatment administration. Pregnancy tests will also be performed at the beginning of each cycle thereafter (as described in the protocol), and continue monthly up to 6 months after the end of treatment per the duration of required contraception.

Duration of required contraception for female patients in this clinical study should start from the screening visit until 6 months after last dose of the latest administered study drug.

Female patients must agree to one of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - Nonhormonal intrauterine device (IUD)
  - Hormonal IUD (must be used in conjunction with a barrier method)
  - Bilateral tubal occlusion (upon medical assessment of surgical success)
  - Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone

- Transdermal contraceptive patch
- Contraceptive vaginal ring
- Subdermal contraceptive implant

- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

3) Contraception Requirements for Male Patients

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure to the patient's seminal fluid and pose a potential risk to an embryo/fetus. Male patients with female partners of childbearing potential must use condoms during treatment until 6 months after last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months after the last study drug dose. Study drug must be discontinued immediately.

Male patients whose partner has become pregnant or suspects she is pregnant from start of study to 6 months after the last the study drug dose must also report the information to the investigator. Partner pregnancy information will not be collected in this study; however, the investigator should reinforce proper contraception use with the study patient if a partner pregnancy is reported. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 5. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 6. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

{Oken 1982}

Appendix 7. Response Evaluation Criteria in Solid Tumors (RECIST V1.1)

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

Appendix 8. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

SPECIMEN

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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SPECIMEN

Appendix 9. 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

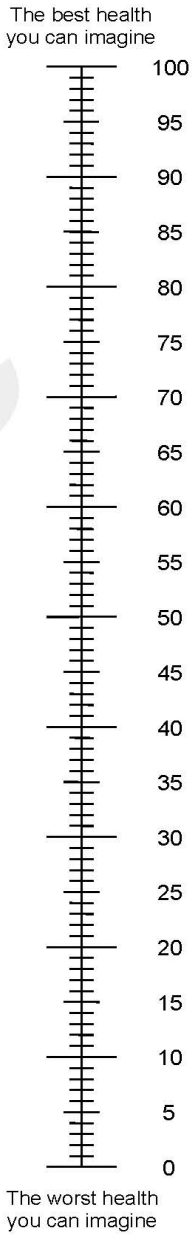
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Sample

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Sample

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Appendix 10. FACT Colorectal Symptom Index (FCSI)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix 11. Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at Least 1 Country Following EU Regulation No. 536/2014	To Be Used per Label (Marketed Products Only)
Magrolimab	Study Drug	No	NA
Bevacizumab	Study Drug	Yes[a]	Yes
Leucovorin Calcium	Study Drug	Yes[a]	Yes
Levoleucovorin Calcium	Study Drug	Yes[a]	Yes
Fluorouracil	Study Drug	Yes[a]	Yes
Irinotecan Hydrochloride	Study Drug	Yes[a]	Yes
Acetaminophen	AxMP	Yes[a]	Yes
Diphenhydramine	AxMP	Yes[a]	Yes
Dexamethasone	AxMP	Yes[a]	Yes

AxMP = auxiliary medicinal product; EU = European Union; NA = not applicable
a Rationale described in Sections 1.3 and 1.3.3.

Appendix 12. Country-Specific Requirements

Not applicable.

Appendix 13. Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsection below (from most recent amendment to oldest), with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 4 to this amendment will be made available upon the publication of this protocol.

Amendment 5 (31 October 2023)

Rationale for Key Changes Included in Amendment 5	Affected Sections
Clarified that all the safety laboratory assessments should be conducted at the central laboratory unless local laboratory testing is specified.	Tables 2 and 9
Updated to incorporate corticosteroids as auxiliary medicinal products for this clinical study.	Section 1.3.3 and Appendix 11
Amended to include overlapping toxicities reported in Version 12 of the IB.	Section 1.6
Clarified the efficacy assessments regarding confirmation of disease progression.	Table 2 and Sections 3.4.1 and 6.3.10
Changed the grade for peripheral neuropathy from more than 1 to more than 2 in exclusion criterion No. 9.	Section 4.3
CCI [redacted]	Section 4.3
CCI [redacted]	Section 4.3
Removed the requirement of sponsor's approval for withholding magrolimab in case of treatment-emergent and/or related adverse events.	Section 5.5.2
Updated to incorporate guidance for the use of corticosteroids as premedication for the first few infusions of magrolimab.	Section 5.5.3
Updated to add clarifications for dose administration.	Tables 5 and 6
Updated to allow flexibility in bevacizumab and FOLFIRI infusion times per local practice.	Section 5.6
Specified the computed tomography (CT) and magnetic resonance imaging (MRI) scan sites and clarified the requirement for scans at end of treatment.	Section 6.3.10
Text regarding patients with low baseline hemoglobin level moved from Section 7.8.1.3.1 to Section 7.8.1.2 to better align the information with the section headers.	Section 7.8.1
Replaced "blood" with "extended RBC" to align with the updated investigator's brochure.	Section 7.8.1.1
Updated the Management of Infusion-Related Reactions information [redacted].	Section 7.8.1.4

Rationale for Key Changes Included in Amendment 5	Affected Sections
Added 2 new sections "Severe Neutropenia" and "Serious Infections" to the Toxicity Management section, to provide guidelines for dose delay and discontinuation in case of severe neutropenia and serious infections.	Sections 7.8.1.7 and 7.8.1.8
Incorporated changes from Administrative Amendment 4.0.1.	Sections 7.8.1.1 and 7.8.1.3, and Appendix Table 1
Incorporated changes from Administrative Amendment 4.0.2.	Table 2, Section 5.5.2, and Appendix Table 1
Specified the version of RECIST as 1.1.	Throughout, as needed
Minor changes to correct typographic errors and provide clarification.	Throughout, as needed

Amendment 4 (21 June 2023)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Added a Gilead Data Review Committee to monitor safety data at prescribed intervals and provided stopping rules based on Grade 4 or 5 treatment-related adverse events.	Sections 3.1.2.1 and 8.12
Required therapy for inclusion updated to allow prior capecitabine combined with oxaliplatin.	Synopsis, Sections 4.2 and 4.3
Optional prescreening consent added for sample collection.	Table 1, Section 6.2.1
Added further laboratory testing.	Tables 2 and 10, Sections 6.3.9 and 7.8.1.3
Timing of doses for combination therapy updated to providing flexibility of dosing over 2 days.	Sections 5.5 and 5.6
Effects of magrolimab on pregnancy and hormonal contraception updated based on current data.	Appendix 4
Clarification of adverse event screening assessment.	Table 1
Clarification of standard of care procedure language.	Section 6.2
Clarification of screening procedure language.	Section 6.3.10
Clarification added that leucovorin dose may be adjusted based on local guidelines.	Section 5.5
Clarification added that patient-reported outcome assessments can be waived if there is a barrier to completion.	Table 2 and Section 6.3.14
Option for local sourcing of bevacizumab and FOLFIRI added.	Sections 5.3.2 and 5.4.2
Guidance for reporting temperature excursions during magrolimab storage added.	Section 5.2.3
Introduction updated based on current clinical practice.	Section 1.3.1
Minor changes to correct typographic errors.	Throughout, as needed

Appendix 14. Sponsor Signature Page

GILEAD SCIENCES, INC.
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A Phase 2, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination With Bevacizumab and FOLFIRI Versus Bevacizumab and FOLFIRI in Previously Treated Advanced Inoperable Metastatic Colorectal Cancer (mCRC)

GS-US-587-6156, Amendment 5, 31 October 2023

APPROVAL OF CLINICAL STUDY PROTOCOL

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD	*[See appended electronic signature]*
Primary Medical Monitor	Signature
[See appended electronic signature]	
Date	

Prot GS-US-587-6156 amd-5

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	01-Nov-2023 06:50:28