Title Page

Protocol Title:	**A randomized Phase 2 study of ompenaclid versus placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated *RAS* mutant advanced or metastatic colorectal cancer**
Brief Title:	**A study to investigate response to ompenaclid combined with FOLFIRI plus bevacizumab in patients with advanced or metastatic colorectal cancer**
Compound:	Ompenaclid (RGX-202-01)
Indication:	*RAS* mutant advanced or metastatic colorectal cancer
Study Sponsor:	Inspirna, Inc. 310 East 67th Street Suite 1-12 New York, NY 10065 Telephone: 646-590-9064
Protocol Number:	RGX-202-002
Study Phase:	Phase 2
Regulatory Agency Identifying Numbers:	IND 138812 EU CT No. 2023-503356-27-00 UTN U1111-1287-0704 *NCT05983367*
Version:	Version 2.0
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PROTOCOL APPROVAL SIGNATURE

Protocol Title: **A randomized Phase 2 study of ompenaclid versus placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated *RAS* mutant advanced or metastatic colorectal cancer**

Protocol Number: RGX-202-002

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonization (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements. Compliance with GCP standards provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Sponsor Signatory:

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Signature

November 22, 2023
Date

Contact Information for the Sponsor and Medical Monitor are provided separately.

DOCUMENT HISTORY			
Document	**Amendment Scope; Region/Country Identifier (if applicable)**	**Protocol Version**	**Date**
Original Protocol	Not Applicable	1.0	02-Feb-2023
Amendment 1	All Countries	2.0	20-Nov-2023

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Abbreviations and Definitions

Abbreviation	Description
5-FU	5-fluorouracil
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
[redacted]	[redacted]
BID	twice daily
bpm	beats per minute
CKB	creatine kinase B
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTA	clinical trial applications
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	clinical trials information system
CV	cardiovascular
DBP	diastolic blood pressure
DCR	disease control rate
DMC	Data Monitoring Committee
dMMR	mismatch repair deficiency
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DRE	disease-related events
ECG	electrocardiogram

Abbreviation	Description
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EOT	end of treatment
EU	European Union
EU CT	European Clinical Trial
FDA	Food and Drug Administration
FOLFIRI	irinotecan, leucovorin, and 5-fluorouracil
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practices
hERG	human ether-a-go-go related gene
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IVRS	interactive voice response system
IWRS	interactive web response system
LC-MS	liquid chromatography-mass spectrometry
LVEF	left ventricular ejection fraction
MH	Mantel-Haenszel
MRI	magnetic resonance imaging
MSI-H	high microsatellite instability
MTD	maximum tolerated dose

Abbreviation	Description
MUGA	multigated acquisition
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
ORR	overall response rate
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QTc	QT interval corrected for heart rate
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SoA	schedule of activities
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal range
USA	United States of America
WOCBP	woman of childbearing potential

1 Protocol Summary

1.1 Synopsis

Protocol Title: A randomized Phase 2 study of ompenaclid versus placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated *RAS* mutant advanced or metastatic colorectal cancer

Brief Title: A study to investigate response to ompenaclid combined with FOLFIRI plus bevacizumab in patients with *RAS* mutant advanced or metastatic colorectal cancer

Sponsor Protocol No.: RGX-202-002

Study Phase: Phase 2

Sponsor: Inspirna, Inc.

Regulatory Agency Identifier Numbers: IND No. 138812, EU CT No. 2023-503356-27-00, UTN U1111-1287-0704

Rationale:

Inspirna is developing ompenaclid (the hemi-succinate salt of RGX-202, [redacted] an orally bioavailable, small molecule inhibitor of the creatine transporter, SLC6a8, for the treatment of patients with gastrointestinal malignancies. [redacted] Metastatic colon cancer cells activate the creatine pathway by upregulating SLC6a8 and creatine kinase B (CKB) to fuel survival and metastatic progression. In animal models of colon cancer, knockdown of SLC6a8 or CKB suppresses metastatic colonization to the liver, while overexpression of CKB enhances metastatic colonization. Ompenaclid interferes with this pathway by inhibiting the SLC6a8 creatine transporter and thus reducing intracellular creatine and adenosine triphosphate (ATP) levels in cancer cells.

In an ongoing study (RGX-202-001), multiple oral doses of ompenaclid as a single agent or in combination with irinotecan, leucovorin, and 5-fluorouracil (5-FU) (FOLFIRI) ± bevacizumab have been evaluated in patients with unresectable or metastatic gastrointestinal tumors. Among the patients with previously treated colorectal cancer (CRC) harboring *RAS* mutations, the overall response rate (ORR) indicated a treatment benefit and 3000 mg twice daily (BID) of ompenaclid was determined to be optimal for achieving efficacious systemic exposure.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the efficacy of ompenaclid versus placebo	Overall response rate (ORR)
Secondary	
To compare additional efficacy parameters of ompenaclid versus placebo	Progression-free survival (PFS) (key secondary objective) Overall survival (OS) Duration of response (DoR) Disease control rate (DCR)
To determine the safety of treatment with ompenaclid	Adverse events, performance status (Eastern Cooperative Oncology Group [ECOG]), physical examinations, clinical laboratory values, vital signs, electrocardiogram
To assess the pharmacokinetics (PK) of ompenaclid	Steady state concentration
To evaluate exploratory biomarkers that may correlate with efficacy outcomes	CKB levels identified in baseline tumor samples

Overall Design Summary:

- This is a Phase 2, randomized, double-blind, placebo-controlled study.
- The study population will consist of patients with previously treated *RAS* mutant advanced or metastatic CRC who had progression of disease after receiving a first line oxaliplatin based chemotherapy regimen and who are candidates for second line therapy.
- All patients will receive standard of care (SOC) treatment with leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) and bevacizumab. Patients randomized to the investigational medicinal product (IMP) will self-administer five 600-mg IMP tablets (3000 mg total) orally, BID on Days 1 to 28 of each 28-day cycle unless otherwise instructed by the investigator. Patients randomized to placebo will self-administer a matching placebo dose.

- The primary efficacy endpoint of the study is ORR. The secondary efficacy endpoints are PFS, OS, DoR, and DCR. Steady state PK will be evaluated. Safety will be monitored throughout the study.

- An independent Data Monitoring Committee (DMC) will conduct unblinded interim analyses of safety approximately every 6 months following randomization of the first patient. Additionally, the DMC will conduct unblinded interim analyses of efficacy, the timing and scope of which will be outlined in the DMC Charter.

Brief Summary:

The purpose of this study is to measure tumor response to treatment with ompenaclid in patients with previously treated *RAS* mutant advanced or metastatic CRC. All patients will receive treatment with FOLFIRI and bevacizumab. In addition, patients will be randomized to receive either ompenaclid 3000 mg BID or matching placebo (herein referred to as Study Drug). Each treatment cycle is 28 days in duration.

Each patient will continue with their assigned study treatment until progressive disease (PD), or another discontinuation criterion is met.

Patients will be required to attend the clinic for screening evaluations prior to randomization. During each 28-day treatment cycle, patients will have visits on Days 1 and 15 for study procedures including the FOLFIRI and bevacizumab infusions. Patients will return to the clinic on Days 3 and 17 to disconnect from the 5-FU infusion unless a home-based nursing service or other local care has been arranged. Follow-up to determine post-treatment safety and survival will be conducted by telephone.

Number of Participants:

Approximately 70 patients are planned to be randomized 1:1 to Study Drug (ompenaclid or placebo) treatment.

Study Arms and Duration:

Patients will attend a screening visit between 28 days (Day -28) and 1 day (Day -1) prior to randomization. The 28-day treatment cycle will start on Cycle 1 Day 1. Treatment cycles will continue until PD, or another discontinuation criterion is met, including unacceptable toxicity, voluntary withdrawal from treatment, or closure of the study by the Sponsor; no maximum duration of therapy has been set. An end of treatment (EOT) assessment will be performed within 21 days following the last dose of Study Drug and a safety follow-up phone call will

occur 30 days (±3 business days) after the last dose of Study Drug. Thereafter, patients should be contacted approximately every 90 days (±14 days) for up to 2 years from last subject enrolled, or until withdrawal of consent, loss to follow-up, death, or study closure, whichever occurs first. Data to be collected during this extended follow-up includes the patients' survival status, disease status, and anticancer treatment. If the patient discontinued for a reason other than radiographic PD, additional scan data may also be collected, if possible, until documented radiographic PD, initiation of new anticancer treatment, or study closure, whichever occurs first. In patients who become candidates for surgery or radiation with curative intent during the study, post-EOT follow-up may include tumor measurements and disease response assessments, and documenting any anti-cancer therapies until development of radiographic or clinical PD.

An independent DMC has been appointed for this study. It is comprised of a group of independent experts who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring this particular study.

Inclusion and Exclusion Criteria

To be randomized in this study, patients must **meet** the following criteria during the screening period:

1. Advanced disease, defined as cancer that is either metastatic or locally advanced and unresectable and for which additional radiation therapy or other locoregional therapies are not considered feasible.

2. Progression of disease after receiving only 1 prior regimen considered standard of care for CRC in the advanced/metastatic setting, and it must have been an oxaliplatin-containing regimen. Patients who have mismatch repair deficiency/ high microsatellite instability (dMMR/MSI-H) CRC must have also received prior treatment with pembrolizumab or a Food and Drug Administration (FDA)/European Union (EU)-approved programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitor. Patients may have received prior treatment with bevacizumab or an European Medicines Agency (EMA)-approved biosimilar. Patients who developed metastatic CRC within 12 months of completion of adjuvant oxaliplatin and 5-FU based therapy are also eligible.

3. Histologic or cytologic evidence of a malignant colorectal tumor of adenocarcinoma or poorly differentiated histology that is laboratory-confirmed to be *RAS* mutant. Confirmation of *RAS* mutant status by liquid biopsy is acceptable only if the tumor

sample is not available and the liquid biopsy was performed before initiation of the patient's prior treatment regimen. Patients who convert to *RAS* mutant status after initially having documented wild-type histology are not eligible.

4. Disease that is measurable by standard imaging techniques by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. For patients with prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.

5. At least 18 years old.

6. ECOG performance score ≤ 1.

7. Adequate baseline organ function, as demonstrated by the following:

    a. Calculated creatinine clearance > 60 mL/min per institutional standard.

    b. Serum albumin ≥ 2.5 g/dL.

    c. Bilirubin ≤ 1.5 × institutional upper limit of normal range (ULN).

    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional ULN; patients with hepatic metastases may have AST and ALT ≤ 5 × institutional ULN.

    e. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.

    f. Hemoglobin ≥ 8 g/dL and no red blood cell (RBC) transfusions during the prior 14 days.

    g. Platelet count ≥ 100×10^9/L and no platelet transfusions during the prior 14 days.

8. If not taking warfarin (or similar vitamin K inhibitor) the following values are required: international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN and either partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT) ≤ 1.5 × ULN. Patients on warfarin (or similar vitamin K inhibitor) may be included if on a stable dose with a therapeutic INR < 3.5.

9. Left ventricular ejection fraction (LVEF) ≥ 45% as determined by either echocardiography (ECHO) or multigated acquisition (MUGA) scanning.

10. Woman of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 2 weeks prior to treatment.

11. Men and WOCBP must agree to use acceptable contraceptive methods for the duration of time on the study and continue to use acceptable contraceptive methods for at least 6 months from the last dose of bevacizumab or 2 months after the last dose of ompenaclid, whichever is longer.

12. Provides signed informed consent prior to initiation of any study-specific procedures or treatment.

13. Able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.

Potential patients who meet any of the following criteria at screening will be **excluded** from the study:

1. Persistent clinically significant toxicities (Grade ≥ 2) from previous anticancer therapy. Excluded are Grade 2 chemotherapy-related neuropathy and alopecia which are permitted and Grade 2 laboratory abnormalities if they are not associated with symptoms, are not considered clinically significant by the Investigator, or can be managed with available medical therapies.

2. CRC with histology (or component of histology) consistent with small cell, neuroendocrine, or squamous carcinoma, or lymphoma.

3. Received treatment with chemotherapy, external-beam radiation, or other systemic anticancer therapy within 14 days prior to study therapy administration (42 days for prior nitrosourea or mitomycin-C).

4. Received treatment with an investigational systemic anticancer agent within 5 half-lives of the investigational systemic therapy or within 28 days, whichever is shorter prior to Study Drug administration.

5. Has an additional active malignancy that may confound the assessment of the study endpoints. Patients with a past cancer history with substantial potential for recurrence must be discussed with the Medical Monitor before study entry. Patients with the following concomitant neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma *in situ* (including transitional cell carcinoma, cervical intraepithelial neoplasia, and melanoma *in situ*), organ-confined prostate cancer with no evidence of progressive disease.

6. Clinically significant cardiovascular disease: e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension (defined as systolic blood pressure [SBP] > 160 or diastolic blood pressure [DBP] > 90), or clinically significant arrhythmias not controlled by medication.

7. Known active or suspected brain or leptomeningeal metastases. Central nervous system (CNS) imaging is not required prior to study entry unless there is a clinical suspicion of CNS involvement.

8. Uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.

9. Pregnant or breast feeding.

10. Evidence of muscular dystrophies or ongoing muscle pathology.

11. Oxygen-support requirements.

12. QTc > 470 msec.

13. Physical abnormality or medical condition that limits swallowing multiple pills or has a history of non-adherence to oral therapies.

14. A gastrointestinal (GI) condition that may significantly alter absorption.

15. Clinically significant ascites (i.e., requiring paracentesis within the preceding 28 days or treatment with pain medication).

16. Any medical condition which, in the opinion of the Investigator, places the patient at an unacceptably high risk for toxicities.

17. Known dihydropyrimidine dehydrogenase (DPD) deficiency or is on treatment with DPD inhibitors, including sorivudine or its chemically related analogues such as brivudine, within 4 weeks prior to the start of FOLFIRI treatment.

18. Requires treatment with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors.

19. Previously received FOLFIRI or other irinotecan containing treatment regimens.

20. Marked proteinuria (≥ 2 g/24 hours) and/or nephrotic syndrome. Patients with a proteinuria 2+ or greater urine dipstick reading should undergo further assessment, e.g., a 24-hour urine collection.

21. History of acute or subacute intestinal occlusion, unless such an event occurred only around the time of initial diagnosis or development of metastatic disease, or from chronic inflammatory bowel disease or chronic diarrhea.

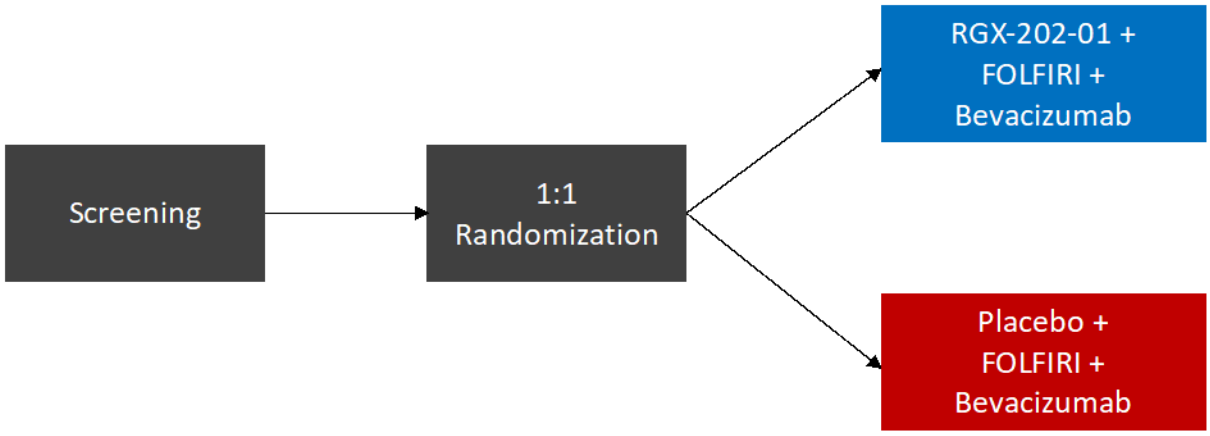
22. Severe, non-healing wounds, ulcers, or bone fractures.

23. History of hemodynamically significant pulmonary embolism within 6 months prior to inclusion in the study.

24. History of hemorrhagic diathesis or tendency towards thrombosis that is not optimally managed, with the exception of tumor bleeding before tumor resection surgery.

1.2 Schema

Figure 1–1 Study Design



FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil

1.3 Schedule of Activities (SoA)

Table 1-1 Schedule of Activities (SoA)

Assessments and Procedures	Screening (D -28 to D-1)	Intervention Period (28 days)				EOT[b]	Safety and Long-term Follow-up[c] (Post-EOT)	Notes
		D1[a]	D3	D15	D17			
Informed consent	X							
Inclusion and exclusion criteria	X							
Archival tumor sample (5-15 slides or block)	X							Confirmation of availability of archival tissue at Screening required; sample may be submitted following randomization. If samples are to be obtained from another institution, every attempt should be made to collect and submit the samples as soon as possible following randomization. If a tumor block is submitted, slides will be prepared by the central lab right away and the block will be returned to the study site as soon as possible.
Demography	X							
Pregnancy test	X					X		Urine or serum pregnancy test within 2 weeks prior to treatment for WOCBP or closer to treatment start date as per local/institutional

Assessments and Procedures	Screening (D -28 to D-1)	Intervention Period (28 days)				EOT[b]	Safety and Long-term Follow-up[c] (Post-EOT)	Notes
		D1[a]	D3	D15	D17			
								regulations and at the EOT visit. See Section 8.3.6
LVEF (ECHO or MUGA)	X							See Section 8.1
Vitals signs and weight	X	X		X				
Physical examination	X	X		X				Height measured at Screening only
Concomitant medications	X	X		X		X	X	
Medical and cancer history (including prior therapy)	X	X						
ECOG performance status	X	X						
Local Laboratory tests (Safety)	X	X		X[d]				Includes hematology, chemistry, urine dipstick, and coagulation parameters[d] as specified in Section 8.3.5
PK sample				X				Samples to be collected pre-dose at Cycles 1 and 2 only. Patients should be instructed not to take their morning dose of study drug at home before coming to the clinic to ensure PK samples are collected pre-dose. The

Assessments and Procedures	Screening (D -28 to D-1)	Intervention Period (28 days)				EOT[b]	Safety and Long-term Follow-up[c] (Post-EOT)	Notes
		D1[a]	D3	D15	D17			
								morning dose of study drug should be brought to the clinic and taken following sample collection.
12-lead ECG	X			X				ECG required only at Screening and on Day 15 in Cycle 2; more frequently if clinically indicated. See Section 8.3.3
CT/MRI for tumor measurement and disease assessment by RECIST 1.1 criteria[e]	X	X				X	X	Baseline imaging required within 28 days prior to the first dose of Study Drug (Cycle 1 Day 1). Follow-up imaging is required approximately every 8 weeks (+/- 5 business days) after Randomization. See Section 8.2.
Randomization		X						Cycle 1 only
Study Drug		←==========			==========→			Ompenaclid/matching placebo will be administered BID PO on Days 1 to 28 each cycle. Study drug should be taken in the morning and evening approximately 12 hours apart.
FOLFIRI administration		X	X[f]	X	X[f]			Administered intravenously as follows: irinotecan 180 mg/m^2 according to institutional standard practice (e.g., over 60-90 minutes) concurrently with leucovorin 400 mg/m^2, and then 5-FU 2400 mg/m^2 over 46 hours on Days 1 and 15 of each 28-day cycle. Sites may discuss alternative 5-FU administration regimens with the study Medical Monitor, e.g., bolus dosing.

Assessments and Procedures	Screening (D -28 to D-1)	Intervention Period (28 days)				EOT[b]	Safety and Long-term Follow-up[c] (Post-EOT)	Notes
		D1[a]	D3	D15	D17			
Bevacizumab administration		X		X				Administered as 5 mg/kg, Days 1 and 15 in each cycle
AE/SAE review		←==========			==========→	X	X	EOT safety follow-up by telephone 30 days after last dose of Study Drug. Study Drug-related SAEs should continue to be followed, where possible.
Survival status and new cancer therapy (post-EOT)							X	Contact by phone approximately every 90 days until withdrawal of consent, loss to follow-up, death, or study closure, whichever occurs first.

Abbreviations: AE = adverse event; BID = twice daily; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FOLFIRI = irinotecan, leucovorin, and 5-fluorouracil; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetics; PO = orally; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of childbearing potential.

a. Screening procedures may be performed within 28 days of Cycle 1 Day 1 (C1D1) and screening safety assessments completed within 3 business days of C1D1 do not need to be repeated prior to randomization. Procedures for all other visits should be completed within ±3 business days of the target visit day unless otherwise specified, e.g., PK sample collection. Safety assessments, including physical exams, may be performed up to 3 business days prior to Day 1 and Day 15 of each cycle to allow for medical review prior to Study Drug dispensation and SOC infusions.

b. The EOT visit should be conducted as soon as possible following the last dose of Study Drug but may be performed up to 21 days after discontinuation of treatment. In the event a patient is unable to return to the clinic for EOT assessments due to death, hospitalization, or admittance to hospice care, results from outside assessments may be entered in EDC or the visit may be marked as "not done" and all efforts should focus on obtaining any further safety follow-up related to new or ongoing Study Drug-related AEs and SAEs and follow-up of disease and survival status. CT/MRI to be performed at this visit unless radiographic PD was previously documented, or a scan is available within 28 days of the visit.

c. A Safety Follow-up should be conducted by phone 30 days (±3 business days) after the last dose of Study Drug. Thereafter, patients should be contacted approximately every 90 days (±14 days) for up to 2 years from last subject enrolled, or until withdrawal of consent, loss to follow-up, death, or study closure, whichever occurs first. Data to be collected during this extended follow-up includes the patients' survival status, disease status, and anticancer treatment. If the patient discontinued for a reason other than radiographic PD, additional scan data may also be collected, if possible, until documented PD, initiation of new anticancer treatment, or study closure, whichever occurs first.

d. Coagulation tests at Screening and Cycle 1 Day 1 only. Either PT or INR may be measured, depending on institutional standards. PT/INR should be checked weekly for patients on warfarin (or similar vitamin K inhibitor) or per standard of care. It is recommended that the smallest appropriate sampling tubes be used to curtail blood loss due to phlebotomy.
e. Tumor measurements and disease response assessments also are to be performed at the EOT visit unless radiographic PD was previously documented. In patients who become candidates for surgery or radiation with curative intent during the study, post-EOT follow-up may include tumor measurements and disease response assessments and documenting any anti-cancer therapies until development of radiographic or clinical PD.
f. Patients will return to clinic on Days 3 and 17 to disconnect from the 5-FU infusion unless a home-based nursing service or other local care close to the patient's home has been arranged.

2 Introduction

Ompenaclid (the hemi-succinate salt of RGX-202, [redacted] is an orally bioavailable, small molecule inhibitor of the creatine transporter, SLC6a8, for the treatment of patients with gastrointestinal malignancies. [redacted]

2.1 Study Rationale

Metastatic colon cancer cells activate the creatine pathway by upregulating SLC6a8 and CKB to fuel survival and metastatic progression (Loo 2015). In animal models of colon cancer, knockdown of SLC6a8 or CKB suppresses metastatic colonization to the liver, while overexpression of CKB enhances metastatic colonization (Loo 2015). Ompenaclid interferes with this pathway by inhibiting the SLC6a8 creatine transporter and thus reducing intracellular creatine and ATP levels in cancer cells.

RAS mutations, which are found in ~45% of CRCs, can induce significant metabolic dysregulation in cancer cells. In an ongoing study (RGX-202-001), multiple oral doses of ompenaclid as a single agent or in combination with FOLFIRI ± bevacizumab have been evaluated in patients with unresectable or metastatic gastrointestinal tumors. Among the patients with previously treated CRC harboring *RAS* mutations, the ORR indicated a treatment benefit and 3000 mg BID of ompenaclid was determined to be optimal for achieving efficacious systemic exposure.

2.2 Background

Metastatic CRC that is resistant to the currently approved methods of treatment is recognized as a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared towards discovering and developing new treatment regimens with modes of action distinct from those of established agents and with the ability to target subclasses of CRC, such as those associated with *RAS* mutations.

Ompenaclid (the hemi-succinate salt of RGX-202, [redacted], is an orally bioavailable, small molecule inhibitor of the creatine transporter, SLC6a8, for the treatment of patients with gastrointestinal malignancies. [redacted]

In an ongoing study (RGX-202-001), 3000 mg BID of ompenaclid was determined to be optimal for achieving efficacious systemic exposure and demonstrated the potential for clinical benefit to the patients with previously treated *RAS* mutant advanced or metastatic CRC.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ompenaclid is provided in the Investigator's Brochure.

2.2.1 Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

2.2.1.1 Pharmacokinetics

Ompenaclid is not a substrate of the efflux transporters P-gp or breast cancer resistance protein (BCRP) in MDCKII cells or vesicles expressing P-gp or BCRP; however, there was evidence suggesting that ompenaclid is a substrate of an uptake transporter that is endogenously expressed in the MDCKII cell line.

Metabolism does not appear to be a major clearance mechanism for this compound as ompenaclid does not appear to interact with cytochrome P450 (CYP) enzymes and is not metabolized by liver hepatocytes in any species tested, nor is it an inhibitor of the common human ATP-binding cassette or solute carrier transporters.

Since ompenaclid does not appear to be metabolized, therefore excretion of the parent unchanged is likely the main clearance mechanism. In the dose regimen finding studies in the rat and dog, significant amounts of ompenaclid were found in the urine, indicating that renal excretion is a likely clearance mechanism for this compound.

2.2.1.2 Safety Pharmacology

Ompenaclid inhibited human ether-a-go-go related gene (hERG) current by 1.0% at 100 μM and 3.8% at 1000 μM and was not statistically significant when compared to vehicle control values. As inhibition greater than 50% was not observed, the IC_{50} for the inhibitory effect of ompenaclid on hERG potassium current was not calculated but was estimated to be greater than 1000 μM.

2.2.1.3 Toxicology

Nonclinical studies were conducted *in vitro* and *in vivo* in Sprague-Dawley rats and Beagle dogs to evaluate the potential toxicity of ompenaclid. Ompenaclid was given via oral gavage administration, which is the route proposed for use in the initial clinical study.

In the non-Good Laboratory Practices (GLP) single-dose escalation studies, the maximum tolerated dose (MTD) of ompenaclid via a single oral dose in rats and dogs was 1000 mg/kg.

In the 7-day non-GLP range-finding study in rats and dogs, animals were given ompenaclid orally at dose levels of 100, 300, and 1000 mg/kg/day. In both studies, ompenaclid was well

tolerated and all animals survived until scheduled necropsy and test article-related effects were mainly observed in 300 and 1000 mg/kg/day groups. In rats, these effects included slightly decreased mean body weights, body weight gains and food consumptions, as well as minor changes in clinical chemistry and hematology parameters. In dogs, these effects included emesis, loose feces, minor changes in clinical chemistry parameters, as well as minimally increased liver weight. No target organs were identified in either species.

A 4-week GLP rat toxicity study with a two-week recovery period was conducted at dose levels of 0, 100, 600, and 1330 mg/kg/day, and also included evaluation of the central nervous and respiratory systems. There were no test article-related mortalities, clinical signs or abnormal ophthalmology findings Target organs identified microscopically at doses ≥ 600 mg/kg/day included the liver (minimal hypertrophy) and male reproductive system at doses ≥ 100 mg/kg/day. Delayed spermiation was considered adverse at all dose levels of ompenaclid. At recovery sacrifice in animals administered 1330 mg/kg/day, minimally to mildly delayed spermiation, mild tubular dilatation, minimal epididymal cellular debris and/or epididymal atrophy was observed. These findings were consistent with a partial reversal of testicular changes during the recovery period. There were no treatment-related deaths at oral doses up to 1330 mg/kg/day ompenaclid in Sprague-Dawley rats, thus the STD_{10} is considered to be at least 1330 mg/kg/day. Based on the adverse effects of delayed spermiation in male rats given ≥ 100 mg/kg/day, the no-observed-adverse-effect-level (NOAEL) is undetermined in males and is 1330 mg/kg/day in female rats.

A 4-week GLP dog toxicity study with a 2-week recovery period was conducted at dose levels of 0, 100, 600, and 1330 mg/kg/day, and also included evaluation of the cardiovascular system. There were no test article-related mortalities, or changes in food consumption, body temperature, blood pressure, electrocardiogram (ECG), hematology, coagulation, or urinalysis parameters. Target organs identified microscopically were limited to the liver (dose-related increased hepatocellular rarefaction) at doses ≥ 100 mg/kg/day. This microscopic observation was morphologically indistinguishable from glycogen deposition; however, other subcellular alterations were also possible. None of the hepatic changes was considered adverse. All the changes at terminal sacrifice had fully or partially recovered during the 2-week recovery period. The NOAEL was considered to be 1330 mg/kg/day.

2.2.2 Summary of Findings from Clinical Studies

Ompenaclid is being studied in RGX-202-001, a Phase 1, first-in-human, two stage (dose escalation and expansion) study evaluating multiple doses of orally administered ompenaclid as a single agent and in combination with FOLFIRI ± bevacizumab in patients with advanced gastrointestinal tumors (i.e., locally advanced and unresectable, or metastatic) who have had PD

on available standard systemic therapies or for which there are no standard systemic therapies of relevant clinical impact.

Based on the assessment of preliminary results from study RGX-202-001 obtained as of 05 June 2023 ompenaclid 3000 mg BID has the potential to optimize the likelihood of consistently achieving efficacious systemic exposure and pharmacodynamic biomarkers associated with target management with an acceptable safety profile when combined with FOLIFIRI and bevacizumab. The efficacy results also provide a rationale to enroll patients with previously treated CRC harboring *RAS* mutations. In summary:

- The dose escalation cohorts with single agent ompenaclid or in combination with FOLFIRI ± bevacizumab did not reach an MTD and no dose-limiting toxicities were observed.
- The most common treatment-emergent adverse events (TEAEs) observed with single agent ompenaclid treatment (n = 17 patients) were nausea (8 patients, 47%), vomiting (7 patients, 41%), fatigue (5 patients, 29%), diarrhea (4 patients, 24%), and decreased appetite (4 patients, 24%). Grade ≥ 3 TEAEs were observed in 8 patients with the most frequent being hypertension (n = 2, 12%), nausea (n = 1, 6%), and vomiting (n = 1, 6%).
- The most common TEAEs observed with ompenaclid 2400 mg BID or 3000 mg BID in combination with FOLFIRI and bevacizumab (n = 38) were nausea (18 patients, 47%), fatigue (10 patients, 26%), diarrhea (10 patients, 26%), neutropenia/neutrophil count decreased (6 patients, 16%), constipation (6 patients, 16%), vomiting (5 patients, 13%), decreased appetite (5 patients, 13%), and abdominal pain (5 patients, 13%).
- Grade ≥ 3 TEAEs were observed in 22 patients with the most frequent being neutropenia or neutrophil count decreased (5 patients, 13%), diarrhea (4 patients, 11%), fatigue (4 patients, 11%), nausea (3 patients, 8%), small intestine obstruction (3 patients, 8%), hyperbilirubinemia or blood bilirubin increased (3 patients, 8%), hypertension (2 patients, 5%), pulmonary embolism (2 patients, 5%), and anemia (2 patients, 5%).
- The most common Grade 3-4 TEAEs considered related to ompenaclid were nausea (8%), neutropenia/neutrophil count decreased (6%), diarrhea (6%), and vomiting (5%).
- The GI events and neutropenia in the dose escalation and expansion stages are consistent with those reported for the standard of care therapy with FOLFIRI and bevacizumab in the second line treatment of CRC. Additionally, the overall safety profile of ompenaclid 2400 mg BID or 3000 mg BID in combination with FOLFIRI and bevacizumab showed an acceptable benefit-risk ratio.

- Among 28 patients with advanced (unresectable or metastatic) CRC harboring *RAS* mutations treated with ompenaclid 2400 mg BID or 3000 mg BID in combination with FOLFIRI and bevacizumab as second line therapy, the ORR was 28.6% (8 partial responses [PRs]), or 40.0% among the 20 best response evaluable patients in this subset; with an estimated median PFS of 11.8 months.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ompenaclid may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Gastrointestinal disorders (including nausea, vomiting, and diarrhea) and fatigue are the most frequently reported AEs attributed to ompenaclid as a single agent or in combination with FOLFIRI ± bevacizumab. The safety concerns identified to date are summarized in Section 2.2.2.

Please refer to the Investigational Brochure for additional information regarding potential risks.

2.3.2 Benefit Assessment

Assessments of the benefits of treatment with ompenaclid are ongoing. It is intended to demonstrate that treatment with ompenaclid in combination with FOLFIRI + bevacizumab will provide a safe, effective treatment for patients with previously treated *RAS* mutant advanced or metastatic CRC.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account favorable pre-clinical and clinical safety data generated to date and the measures outlined in this clinical study protocol in Section 6.6 to mitigate toxicities to participants in the study should they occur, the potential risks associated with ompenaclid treatment identified in clinical studies to date are justified by the anticipated benefits that may be afforded to participants with previously treated *RAS* mutant advanced or metastatic CRC.

3 Objectives and Endpoints

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of ompenaclid versus placebo	ORR
Secondary	
To compare additional efficacy parameters of ompenaclid versus placebo	PFS (key secondary objective) OS DoR DCR
To determine the safety of treatment with ompenaclid	Adverse events, performance status (ECOG), physical examinations, clinical laboratory values, vital signs, electrocardiogram
To assess the PK of ompenaclid	Steady state concentration
To evaluate exploratory biomarkers that may correlate with efficacy outcomes	CKB levels identified in baseline tumor samples

4 Study Design

4.1 Overall Design

This is a Phase 2, randomized, double-blind placebo-controlled study of ompenaclid or matching placebo (Study Drug) in combination with standard of care FOLFIRI plus bevacizumab as background therapy in patients with previously treated *RAS* mutant advanced or metastatic CRC. Randomization will be stratified by whether or not the patient received prior treatment with bevacizumab or an EMA-approved biosimilar. In the context of a Phase 2 study with modest enrollment, there is interest in ensuring that the study population is similar to the general population of patients with regards to the randomization stratification factor. Consequently, randomization will be restricted so that approximately 50 patients who received prior treatment with bevacizumab or an EMA-approved biosimilar are enrolled, while approximately 20 patients who did not receive such prior treatment are enrolled.

Written informed consent must be obtained prior to initiating any screening activities, except where patients have agreed to the use of previously available tests completed within 28 days of the planned first dose of Study Drug, e.g., computed tomography (CT)/magnetic resonance imaging (MRI) scans. Screening for study eligibility must be completed within 28 days prior to first dose of Study Drug. Patients who are determined to be eligible, based on Screening assessments, will be randomized in the study. Patients will receive their first dose of Study Drug on Cycle 1, Day 1. A treatment cycle is 28 days in duration. Patients will be randomized in a 1:1 ratio to receive oral administration of the five 600-mg tablets BID of ompenaclid or matching placebo (Study Drug). The intravenous FOLFIRI dose and schedule will be administered according to institutional standard practice; irinotecan 180 mg/m^2 over 60-90 minutes (in patients with UGT1A1*28 or UGT1A1*6 homozygosity, one level dose reduction may be considered [Karas 2022]) concurrently with leucovorin 400 mg/m^2, followed by 5-FU 2400 mg/m^2 over 46 hours, on Days 1 and 15 of each 28-day cycle. Sites may discuss alternative 5-FU administration regimens with the study Medical Monitor, e.g., bolus dosing. The bevacizumab dose of 5 mg/kg will be administered intravenously on Days 1 and 15 of each 28-day cycle.

During the study, patients will attend study center visits and have study evaluations performed as detailed in the Schedule of Activities (Table 1-1). All routine study visits are to be conducted on an outpatient basis.

Patients may continue to receive Study Drug until the development of PD, or another discontinuation criterion is met, including unacceptable toxicity, voluntary withdrawal from treatment, or closure of the study by the Sponsor; no maximum duration of therapy has been set.

After discontinuation of the Study Drug, patients will complete an EOT visit within 21 days after their last dose of Study Drug to complete procedures as outlined in the Schedule of Activities. In the event a patient is unable to return to the clinic for EOT assessments due to death, hospitalization, or admittance to hospice care, results from outside assessments may be entered in the EDC or the visit may be marked as “not done” and all efforts should focus on obtaining any further safety follow-up related to new or ongoing Study Drug-related AEs and SAEs.

An additional Safety Follow-up is to be conducted by telephone 30 days (± 3 business days) after their last dose of Study Drug. Thereafter, patients should be contacted approximately every 90 days (±14 days) for up to 2 years from last subject enrolled, or until withdrawal of consent, loss to follow-up, death, or study closure, whichever occurs first. Data to be collected during this extended follow-up includes the patients’ survival status, disease status, and anticancer treatment. If applicable, sites may also use public records as a source of information to document patient survival status. If the patient discontinued for a reason other than radiographic PD,

additional scan data may also be collected, if possible, until documented PD, initiation of new anticancer treatment, or study closure, whichever occurs first. As applicable, safety information associated with study drug-related SAEs may also be collected during these follow-up contacts.

All patients must have pre-randomization (prior to Study Drug dosing) imaging (CT scan of chest/abdomen/pelvis or MRI, if indicated) and historical tumor biopsy with confirmation that archival tissue is available for submission to a central lab as soon as feasible. Since archival tissue may need to be obtained from an outside institution, randomization may proceed prior to submission of the sample with the understanding that the site will make every effort to obtain and submit the tumor sample in a timely manner.

The time window for screening activities is within 28 days prior to their first Study Drug dose and will differ for radiographic imaging, laboratory assessments, and physical exam and are detailed in Table 1-1. Patients with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements with a ruler) by means of physical examination.

Tumor measurements and disease response assessments also are to be performed approximately 8 weeks (+/- 5 business days) after randomization, and approximately every 8 weeks (+/- 5 business days) thereafter until development of radiographic PD (or other discontinuation criterion).

4.2 Scientific Rationale for Study Design

The design of this study follows the recommendations for the analysis of treatment benefit for patients with metastatic CRC who have been refractory to first-line treatment. The sample size is specified to detect a difference in ORR between the treatment groups (see Section 9.5).

4.3 Justification for Dose

The dose of 3000 mg BID was identified in Study RGX-202-001 to optimize the likelihood of consistently achieving efficacious systemic exposure (see Section 2.2.2).

Study Drug dose modifications within a treatment cycle are to be discussed with the Medical Monitor prior to implementation in order to determine if a lower dose is expected to be tolerated more favorably by the patient, based upon collective safety data from patients treated on the original dose and on lower doses. See Section 6.6.

4.4 End-of-Study Definition

The End of Study for a given patient is defined as the date of the last extended follow-up disease/survival status, or until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

The study is considered complete when sufficient information is available to enable assessment of the primary endpoint and key secondary endpoint. In the weeks subsequent to a determination that sufficient information is available for these assessments, a date for database lock will be assigned, and any outstanding inquiries concerning data elements will be resolved. The Study Completion date will be the date beyond which study data are no longer entered into the primary database (this study completion date generally precedes the date on which the database lock occurs by several weeks/months).

5 Study Population

5.1 Inclusion Criteria

To be randomized in this study, patients must meet the following criteria during the screening period:

1. Advanced disease, defined as cancer that is either metastatic or locally advanced and unresectable and for which additional radiation therapy or other locoregional therapies are not considered feasible.

2. Progression of disease after receiving only 1 prior regimen considered standard of care for CRC in the advanced/metastatic setting, and it must have been an oxaliplatin-containing regimen. Patients who have dMMR/MSI-H CRC must have also received prior treatment with pembrolizumab or an FDA/EU-approved PD-1/PD-L1 inhibitor. Patients may have received prior treatment with bevacizumab or an EMA-approved biosimilar. Patients who developed metastatic CRC within 12 months of completion of adjuvant oxaliplatin and 5-FU based therapy are also eligible.

3. Histologic or cytologic evidence of a malignant colorectal tumor of adenocarcinoma or poorly differentiated histology that is laboratory-confirmed to be *RAS* mutant. Confirmation of *RAS* mutant status by liquid biopsy is acceptable only if the tumor sample is not available and the liquid biopsy was performed before initiation of the patient's prior treatment regimen. Patients who convert to *RAS* mutant status after initially having documented wild-type histology are not eligible.

4. Disease that is measurable by standard imaging techniques by RECIST version 1.1. For patients with prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.

5. At least 18 years old.

6. ECOG performance score ≤ 1.

7. Adequate baseline organ function, as demonstrated by the following:

   a. Calculated creatinine clearance > 60 mL/min per institutional standard.

   b. Serum albumin ≥ 2.5 g/dL.

   c. Bilirubin ≤ 1.5 × institutional ULN.

   d. AST and ALT ≤ 2.5 × institutional ULN; patients with hepatic metastases may have AST and ALT ≤ 5 × institutional ULN.

   e. ANC ≥ 1.5×10^9/L.

   f. Hemoglobin ≥ 8 g/dL and no RBC transfusions during the prior 14 days.

   g. Platelet count ≥ 100×10^9/L and no platelet transfusions during the prior 14 days.

8. If not taking warfarin (or similar vitamin K inhibitor) the following values are required: INR ≤ 1.5 or PT ≤ 1.5 × ULN and either PTT or aPTT ≤ 1.5 × ULN. Patients on warfarin (or similar vitamin K inhibitor) may be included if on a stable dose with a therapeutic INR < 3.5.

9. LVEF ≥ 45% as determined by either ECHO or MUGA scanning.

10. WOCBP must have a negative serum or urine pregnancy test within 2 weeks prior to treatment.

11. Men and WOCBP must agree to use acceptable contraceptive methods for the duration of time on the study and continues to use acceptable contraceptive methods for at least 6 months from the last dose of bevacizumab or 2 months after the last dose of ompenaclid, whichever is longer.

12. Provides signed informed consent prior to initiation of any study-specific procedures or treatment.

13. Able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.

5.2 Exclusion Criteria

Potential patients who meet any of the following criteria at screening will be excluded from the study:

1. Persistent clinically significant toxicities (Grade ≥ 2) from previous anticancer therapy. Excluded are Grade 2 chemotherapy-related neuropathy and alopecia which are permitted and Grade 2 laboratory abnormalities if they are not associated with symptoms, are not considered clinically significant by the Investigator, or can be managed with available medical therapies.

2. CRC with histology (or component of histology) consistent with small cell, neuroendocrine, or squamous carcinoma, or lymphoma.

3. Received treatment with chemotherapy, external-beam radiation, or other systemic anticancer therapy within 14 days prior to study therapy administration (42 days for prior nitrosourea or mitomycin-C).

4. Received treatment with an investigational systemic anticancer agent within 5 half-lives of the investigational systemic therapy or within 28 days, whichever is shorter prior to Study Drug administration.

5. Has an additional active malignancy that may confound the assessment of the study endpoints. Patients with a past cancer history with substantial potential for recurrence must be discussed with the Medical Monitor before study entry. Patients with the following concomitant neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma *in situ* (including transitional cell carcinoma, cervical intraepithelial neoplasia, and melanoma *in situ*), organ-confined prostate cancer with no evidence of progressive disease.

6. Clinically significant cardiovascular disease: e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina, or stroke within 6 months prior to study entry, uncontrolled hypertension (defined as SBP>160 or DBP>90), or clinically significant arrhythmias not controlled by medication.

7. Known active or suspected brain or leptomeningeal metastases. CNS imaging is not required prior to study entry unless there is a clinical suspicion of CNS involvement.

8. Uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.

9. Pregnant or breast feeding.

10. Evidence of muscular dystrophies or ongoing muscle pathology.

11. Oxygen-support requirements.

12. QTc > 470 msec.

13. Physical abnormality or medical condition that limits swallowing multiple pills or has a history of non-adherence to oral therapies.

14. A GI condition that may significantly alter absorption.

15. Clinically significant ascites (i.e., requiring paracentesis within the preceding 28 days or treatment with pain medication).

16. Any medical condition which, in the opinion of the Investigator, places the patient at an unacceptably high risk for toxicities.

17. Known DPD deficiency or is on treatment with DPD inhibitors, including sorivudine or its chemically related analogues such as brivudine, within 4 weeks prior to the start of FOLFIRI treatment.

18. Requires treatment with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors.

19. Previously received FOLFIRI or other irinotecan containing treatment regimens.

20. Marked proteinuria (≥ 2 g/24 hours) and/or nephrotic syndrome. Patients with a proteinuria 2+ or greater urine dipstick reading should undergo further assessment, e.g., a 24-hour urine collection.

21. History of acute or subacute intestinal occlusion, unless such an event occurred only around the time of initial diagnosis or development of metastatic disease, or from chronic inflammatory bowel disease or chronic diarrhea.

22. Severe, non-healing wounds, ulcers, or bone fractures.

23. History of hemodynamically significant pulmonary embolism within 6 months prior to inclusion in the study.

24. History of hemorrhagic diathesis or tendency towards thrombosis that is not optimally managed, with the exception of tumor bleeding before tumor resection surgery.

5.3 Lifestyle Considerations

There are no lifestyle restrictions for the patients in this study.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to Study Drug in the study.

Individuals who do not meet the criteria for participation in this study may be rescreened. Rescreened participants should be assigned a new screening number if they are being rescreened after the initial 28-day screening period. Specific screening tests, e.g., safety labs, may be repeated within the initial screening period without the need for a new screening number.

5.4.1 Screening and Enrollment Log and Participant Identification Numbers

The participant's screening and randomization numbers will be obtained from Medidata Interactive Response Technology (IRT) and recorded in the Screening and Enrollment Log.

Upon randomization, each participant will receive a unique participant identification number. Participant numbers must not be re-used for different participants.

5.5 Criteria for Temporarily Delaying Administration of Study Drug

Study Drug may be interrupted due to treatment-related toxicity for > 1 cycle (i.e., > 28 days). In cases of interruptions for reasons other than AEs and/or in the setting of sustained disease control, delays > 28 days may be acceptable and are to be discussed with the Medical Monitor.

6 Study Intervention(s) and Concomitant Therapy

6.1 Study Interventions Administered

Table 6-1 Study Interventions Administered

Intervention Label	Investigational Medicinal Product	Control	Standard of Care
Intervention Name	ompenaclid	placebo	FOLFIRI and bevacizumab
Intervention Description	oral investigational medication for treatment of metastatic CRC; administered per randomization	not an intervention; administered per randomization	standard of care treatment for CRC administered to all patients
Type	active study drug	control	concomitant treatment
Dosage Formulation	tablet	tablet (matching)	intravenous solution
Unit Dose Strength(s)	600 mg	600 mg (matching placebo)	irinotecan, leucovorin, and 5-FU: mg/m^2 (leucovorin substitutions are acceptable e.g., levoleucovorin) Sites may discuss alternative 5-FU administration regimens with the study Medical Monitor, e.g., bolus dosing. bevacizumab or EMA-approved biosimilar: 5 mg/kg
Dosage Level(s)	3000 mg BID (5 tablets)	3000 mg BID (5 tablets)	irinotecan: 180 mg/m^2 administered according to institutional standard practice (e.g., over 60-90 minutes) concurrently with leucovorin 400 mg/m^2, followed by 5-FU 2400 mg/m^2 over 46 hours, on Days 1 and 15 of each 28-day cycle bevacizumab or EMA-approved biosimilar: 5 mg/kg on Days 1 and 15 of each 28-day cycle
Route of Administration	oral	oral	IV infusion

Intervention Label	Investigational Medicinal Product	Control	Standard of Care
Use	experimental	sham comparator	background intervention
IMP or NIMP/AxMP	IMP	NIMP	AxMP
Sourcing	provided centrally by the Sponsor.	provided centrally by the Sponsor	provided by the study site pharmacy (unless other arrangements are made for the Sponsor to provide)
Packaging and Labeling	Active study drug will be provided in bottles. Each bottle will be labeled per country requirement.	Matching placebo will be provided in bottles. Each bottle will be labeled per country requirement.	Concomitant medications will be provided in commercial packaging (vials and cartons) and will be labeled per regulatory guidelines.

Abbreviations: AxMP = medicinal product not classified as investigational for this study; BID = twice daily; CRC = colorectal cancer; EMA = European Medicines Agency; FOLFIRI = irinotecan, leucovorin, and 5-FU; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

6.2 Preparation, Handling, Storage, and Accountability

Study Drug tablets are packaged into high-density polyethylene (HDPE) bottles. Each bottle contains sixty 600-mg tablets. Bottles are capped with a child-resistant HDPE closure and are induction sealed. All bottles are labeled with a clinical label containing pertinent information for drug receipt and handling. Labeled bottles of Study Drug tablets received from the depot should not be stored above 25°C.

Each study center is to use a Study Drug accountability log to document Study Drug disposition. All items on this form are to be completed in full. The assigned clinical research associate (CRA) is to approve the area where Study Drug is to be stored and accountability records are to be maintained.

Each site will have a unique identification number that will be joined with the patient number to produce a unique participant ID. This ID and the patient's initials (as allowed by local regulations) are to be recorded on each Study Drug accountability log. Each time study personnel dispense Study Drug for a patient, he or she is to record the date dispensed, amount of Study Drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused Study Drug. The CRA is to review Study Drug accountability records and remaining Study Drug supplies during routine monitoring visits. The Investigator is responsible for Study Drug accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).

For additional information on Study Drug handling including dispensing directions refer to the ompenaclid Pharmacy Manual.

6.3 Assignment to Study Intervention

All participants will be centrally randomized using IRT. Each participant will be assigned a unique number (randomization number) that encodes the participant's assignment to one of the 2 arms of the study, according to the randomization schedule generated by the Study Statistician using a validated computer program.

Study Drug will be administered/dispensed at the study visits as summarized in the SoA (Table 1-1). Unscheduled drug dispensation visits may be used as required to ensure adequate supply of Study Drug is available to patients throughout the study.

6.4 Blinding

Participants will be randomly assigned in a 1:1 ratio to receive ompenaclid or placebo (Study Drug). Investigators will remain blinded to each participant's assigned Study Drug throughout the course of the study. To maintain this blind a matching placebo will be provided.

In the event of a quality assurance audit, auditors will be allowed access to unblinded Study Drug records at the sites to verify that randomization/dispensing has been conducted accurately.

Pharmacovigilance staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.5 Study Drug Compliance

Dosing diaries will be provided to the patients for the purpose of recording Study Drug self-administration. The diaries along with unused Study Drug tablets will be returned to the study center at the start of subsequent cycles of therapy to assess compliance. Partially used bottles of returned Study Drug should not be re-dispensed to the participants. Un-opened bottles may be re-dispensed. Dosing diaries will be filed in the patient's source documents.

6.6 Dose Modification

If there is a loss or gain of body weight of ≥ 10% from baseline, or per institutional standard for managing significant weight fluctuations, doses of FOLFIRI and bevacizumab should be recalculated.

6.6.1 Dose Modifications for Study Drug

In the setting of specific toxicities, Study Drug should not be administered on a given day (i.e., doses may be held). Doses held because of AEs should not be made up on subsequent days within or following a cycle. Missed doses should under no circumstances be made-up on a day when the patient is already taking a planned dose (i.e., no "doubling-up" to account for missed doses). If a patient forgets to take a dose at the specified dosing time it may be taken up to 2 hours later. However, if the delay is > 2 hours the dose should be skipped for that day. Additionally, if a patient vomits after taking a dose, the dose should not be re-administered. Dosing should continue the next day per the original schedule.

If Study Drug treatment is interrupted or discontinued at any time, administration of FOLFIRI and bevacizumab may continue unless toxicities specific to FOLFIRI and/or bevacizumab have also been experienced, in which case FOLFIRI and/or bevacizumab should also be interrupted or discontinued. If the Study Drug dose is modified, administration of FOLFIRI and bevacizumab may continue at the original dose unless toxicities specific to FOLFIRI and/or bevacizumab have also been experienced. If the dose of FOLFIRI treatment is modified, administration of Study Drug and bevacizumab may continue at the original dose unless toxicities specific to ompenaclid and/or bevacizumab have also been experienced. Likewise, if the dose of bevacizumab treatment is modified, administration of Study Drug and FOLFIRI may continue at the original dose unless toxicities specific to Study Drug and FOLFIRI have also been experienced.

Dose modifications for Study Drug-related toxicities are summarized in Table 6-2.

Table 6-2 Dose Modifications for Study Drug-Related Toxicities

CTCAE Grade	Dose Adjustment
Grade 1-2	No dose adjustment for subsequent cycles; provide supportive measures per institutional or European Society for Medical Oncology guidelines
Grade ≥3	Hold dosing for up to 4 weeks until resolution to Grade ≤ 1 and resume Study Drug therapy at 2400 mg BID. If another Grade ≥ 3 event occurs, then hold dosing for up to 4 weeks until resolution to Grade ≤ 1 and resume Study Drug therapy at 1800 mg BID. If another ≥ Grade 3 event occurs, permanently discontinue Study Drug.

Adjustments of study drug doses lower than 2400 mg BID should not be made without approval of the Medical Monitor. Dose modifications above this threshold do not require approval by, but do require notification of, the Medical Monitor.

6.6.2 Dose Modifications of FOLFIRI for Treatment Related Toxicity

Dose modifications for FOLFIRI-related toxicity are summarized in Table 6-3. Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the ANC has recovered to $\geq 1.5 \times 10^9$/L, and the platelet count has recovered to $\geq 100 \times 10^9$/L, and treatment-related diarrhea is fully resolved. If the investigator wishes to wait for the ANC to be to $\geq 1.5 \times 10^9$/L in mid cycle treatment that would be acceptable. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to optimizing supportive care (i.e., growth factor support, additional anti emetic, anti-diarrheal agents etc.). If the investigator considers holding a component of the SOC chemotherapy (i.e., irinotecan) the patient may stay in the study as long as they continue to take the Study Drug.

Table 6-3 Dose Modifications for FOLFIRI-Related Toxicity

Toxicity NCI CTC Grade (Value)	**Dose Adjustment During a Cycle of Therapy**	**Dose Adjustment at the Start of Subsequent Cycles of Therapy**
Neutropenia		
Grade 1 (1.5 to 1.999 x 10^9/L)	Maintain dose level	Maintain dose level
Grade 2 (1.0 to 1.499 x 10^9/L)	↓ 1 dose level	Maintain dose level
Grade 3 (0.5 to 0.999 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level	↓ 1 dose level
Grade 4 (< 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as for neutropenia above.	
Diarrhea		
Grade 1 (2–3 stools/day > pretx)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
Grade 2 (4–6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
Grade 3 (7–9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	↓ 1 dose level
Grade 4 (≥10 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other nonhematologic toxicities		

Toxicity NCI CTC Grade (Value)	Dose Adjustment During a Cycle of Therapy	Dose Adjustment at the Start of Subsequent Cycles of Therapy
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
Grade 4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not irinotecan	For mucositis/stomatitis decrease only 5-FU, not irinotecan.

Dose levels of the components of FOLFIRI as a consequence of FOLFIRI-related toxicity are summarized in Table 6-4.

Table 6-4 FOLFIRI Component Dose Levels

Drug	Starting Dose mg/m^2	Dose Level -1 mg/m^2	Dose Level -2 mg/m^2
Irinotecan	180	150	120
Leucovorin Infusion	400	No change	No change
5-FU Infusion	2400	2000	1600

6.6.3 Dose Modifications of Bevacizumab for Treatment Related Toxicity

Dose modifications for bevacizumab-related toxicity are summarized in Table 6-5.

Table 6-5 Dose Modifications for Bevacizumab-Related Toxicity

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Bevacizumab
Wound Healing Complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue Bevacizumab
Hemorrhage	• Grade 3 or 4	Discontinue Bevacizumab
	• Recent history of hemoptysis of ½ teaspoon (2.5 mL) or more	Withhold Bevacizumab
Thromboembolic Events	• Arterial thromboembolism, severe	Discontinue Bevacizumab
	• Venous thromboembolism, Grade 4	Discontinue Bevacizumab
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Bevacizumab

Adverse Reaction	Severity	Dosage Modification
	• Hypertension, severe	Withhold Bevacizumab if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES)	• Any	Discontinue Bevacizumab
Renal Injury and Proteinuria	• Nephrotic syndrome	Discontinue Bevacizumab
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Bevacizumab until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions	• Severe	Discontinue Bevacizumab
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure	• Any	Discontinue Bevacizumab

6.7 Continued Access to Study Drug After the End of the Study

There is no planned intervention after the end of study as patients will continue treatment until PD.

6.8 Treatment of Overdose

For this study, any dose of Study Drug greater than 3000 mg BID within a 24-hour time period will be considered an overdose.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether Study Drug should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Signs and symptoms of an overdose should be reported as AEs. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria (see Section 10.3.2).

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, herbal supplements, other non-traditional medicines) must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prior and Concomitant Medications Review

The Investigator or qualified designee will review prior medication use and record prior medications taken by the participant within 1 month prior to screening.

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the last visit. Concomitant medications will be recorded for 30 days after the last dose of Study Drug (or longer if related to an SAE).

7 Discontinuation of Study Drug and Participant Discontinuation

Discontinuation of specific sites or of the study as a whole are handled as part of the appendix on Governance, Appendix 1, Section 10.1.8.

7.1 Discontinuation of Study Drug

It may be necessary for a participant to permanently discontinue Study Drug. See the SoA (Table 1-1) for data to be collected at the time of discontinuation of Study Drug (EOT Visit) and follow-up and for any further evaluations that need to be completed for patients continuing in the follow-up portion of the study.

Study Drug may be discontinued for any of the following reasons:

- Radiographic progression of disease typically precludes further Study Drug as this will be considered a PD event.
    - After consultation with the Medical Monitor, Study Drug may be continued for a patient who has met the criteria for PD, but in the Investigator's opinion presents

additional evidence of disease control or symptomatic improvement. In this case, the patient must meet the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG or Karnofsky performance status.
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (i.e., symptomatic pleural effusion, spinal cord compression).

  - Patients who meet the aforementioned criteria may continue to receive study therapy until subsequent scans show unequivocal progression by RECIST criteria.

- Occurrence of an unacceptable AE, or clinical deterioration that interferes with activities of daily living.
- Pregnancy.
- Study Drug interruption due to treatment-related toxicity for > 1 cycle (i.e., > 28 days). Interruptions for reasons other than AEs and/or in the setting of sustained disease control, delays > 28 days may be acceptable and are to be discussed with the Medical Monitor.
- Patient requires use of a prohibited concomitant medication or therapy.
- General or specific changes in the patient's condition unacceptable for further treatment within the study parameters, in the judgment of the Investigator:
  - Non-compliance
  - Lost to follow-up
  - Patient withdrawal of consent
  - Sponsor request

All study procedures outlined for the EOT visit are to be completed within 21 days of the last Study Drug dose. In the event a patient is unable to return to the clinic for EOT assessments due to death, hospitalization, or admittance to hospice care, results from outside assessments may be entered in EDC or the visit may be marked not done. The primary reason for Study Drug discontinuation is to be recorded in the electronic case report form (eCRF).

7.1.1 Temporary Discontinuation

See Section 6.6, Dose Modification, for discussion of Study Drug modifications that may lead to stopping and re-starting Study Drug treatment. FOLFIRI and bevacizumab treatment will continue in cases where intolerance is limited to the Study Drug.

7.2 Participant Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at the patient's own request or for any reason (or without providing any reason). A patient may be withdrawn at any time at the discretion of the Investigator for safety or compliance reasons. The patient will be permanently discontinued from the Study Drug and the study at that time.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data and samples collected before such a withdrawal of consent.

If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 Lost to Follow-Up

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. Contact attempts should be documented in the patient's medical record/eCRF.
- Where possible, contact attempts will include 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods.
- Should the patient continue to be unreachable, the patient will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized. Reports from immediate family members and public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participating patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for patient visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 18 mL per cycle (additional samples collected at Screening and in Cycles 1 and 2 for PK). The approximate blood volumes to be collected during the study are described in Table 8-1.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 8-1 Approximate Total Amount of Blood for Each Patient

Timepoint	Parameter	Sample Volume (mL)	Number of Samples	Total Blood Volume (mL)
Screening	Hematology	3.0	1	9.0
	Coagulation	3.0	1	
	Clinical chemistry[a]	3.0	1	
Cycles 1 and 2 – Day 15 only	Plasma PK	3.0	2	6.0
Every 28-day Treatment Cycle	Hematology	3.0	2	18.0
	Coagulation	3.0	2	
	Clinical chemistry[a]	3.0	2	
Total Estimated Blood Volume[b] per Patient = 15.0 mL (Screening +PK) + 18.0 mL per treatment cycle				

[a] Pregnancy tests (women of childbearing potential only) will be performed on the sample collected for clinical chemistry at the Screening Visit in cases where urine testing is not performed.

[b] Excluding repeat laboratory investigations.

Patient Identification Card

All patients will be given a patient identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the patient with a patient identification card immediately after the patient provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the patient identification card.

The patient identification card also contains contact information so that a healthcare provider can obtain information about Study Drug in emergency situations where the Investigator is not available.

Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria and/or safety or efficacy parameters is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1 Administrative and Baseline Procedures

Medical History and Cancer History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within at least the prior 2 years that the Investigator considers to be clinically relevant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

The medical history is to include cancer history, including the patient's primary tumor type, mutation/amplification statuses (e.g., *RAS, BRAF, PDL-1, HER2* and other mutations), current disease stage, date of and disease stage at diagnosis, and all previous treatments, including systemic therapy, radiation therapy, and surgeries, as well as relevant documentation regarding radiological and/or clinical response to such treatment.

Left Ventricular Ejection Fraction

Left ventricular ejection fraction will be obtained using either ECHO or MUGA during Screening.

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1-1).

8.2.1 General Considerations

Imaging of the chest, abdomen, pelvis, and other anatomic areas relevant to the patient's disease is required within 28 days prior to the first administration of Study Drug. CT or MRI are acceptable. Patients with skin, subcutaneous or lymph node metastases may also have tumor evaluations (including measurements, with a ruler) by means of physical examination. During Screening, patients must have disease that is measurable by standard imaging techniques, per RECIST version 1.1. For patients with prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.

Imaging at subsequent time points must include the chest, abdomen, and other anatomic areas relevant to the patient's disease. In selected situations, combination of CT/MRI is acceptable (i.e., CT of chest, MRI of abdomen). It is strongly recommended that the same imaging modalities for each anatomic component be continued throughout the duration of the study. Imaging of extremities is also permitted and is required if significant metastases are present and are optimally evaluated via CT/MRI of an extremity.

Tumor measurements and disease response assessments also are to be performed approximately 8 weeks (+/- 5 business days) after randomization, and then approximately every 8 weeks (+/- 5 business days) thereafter until development of PD. Tumor measurements and disease response assessments are also to be performed at the EOT visit unless radiographic PD was previously documented.

Anatomical measurements (summed across target lesions) will be documented. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the study center, and Investigator's findings will be filed in the patient's source documents. Additionally, all CT/MRI scans will be sent by the study center to an independent central imaging vendor for quality control review and possible central reading at a later date.

8.2.2 Evaluation of Antitumor Response

Evaluation of antitumor response will be by RECIST version 1.1 (Eisenhauer 2009). The procedures are outlined below.

Measurable

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

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

Malignant lymph nodes must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

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

Special considerations regarding lesion measurability:

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

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

- Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

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

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion. When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be

included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.'

Overall response is derived from time-point response assessments (based on tumor burden) as follows:

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

Details for derivation of overall response are summarized in Table 8-2.

Table 8-2 Derivation of Overall Response

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1-1). Safety assessments may be performed up to 3 business days prior to the scheduled day.

8.3.1 Height and Weight

Height will be measured and recorded at screening only. Body weight will be measured, documented in the source documents, and transcribed to the eCRF during screening and on Day 1 and Day 15 of each cycle. Except for Cycle 1 Day 1, this assessment may be performed up to 3 business days prior to the scheduled day.

8.3.2 Physical Examinations

A complete physical examination is to be performed during screening and on Day 1 and Day 15 of each cycle. Except for Cycle 1 Day 1, these assessments may be performed up to 3 business days prior to the scheduled day. Physical examinations are to be conducted by a physician or qualified health professional listed on the delegation log and licensed to perform physical examinations. The complete physical examination is to include assessment of the following:

- General appearance
- Head, eyes, ears, nose, and throat
- Heart and lungs
- Gastrointestinal system (abdomen)
- Musculoskeletal system
- Skin
- Nervous system, includes questions regarding whether the patient is experiencing any numbness and/or pain as well as light touch, sharp touch (skin prick), and temperature, position (proprioception), and vibration sensation testing. Additional nervous assessments are to be performed as appropriate for the patient's condition, at the Investigator's discretion.

It is preferred that all systems are examined; however, it is understood that some sites examine certain systems based on only clinical indication. Protocol violations will therefore not be incurred if certain systems are not examined.

Abnormal physical examination findings that are considered by the Investigator to be clinically significant for a particular patient during Screening and before dosing of Study Drug on Cycle 1 Day 1 are to be reported as part of the patient's medical history. Abnormal, clinically significant

examination findings following initiation of dosing on Cycle 1 Day 1 are to be reported as an AE, if the finding represents a change from Baseline.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3 Standard 12-lead Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (Table 1-1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, RR, and QTc intervals. The ECG results should be reviewed by the investigator or appropriately trained study staff.

8.3.4 Vital Signs

Vital signs, including temperature, heart rate, respiration rate, and blood pressure, and weight are to be measured, documented in the source documents, and transcribed to the eCRF during screening and on Day 1 and Day 15 of each cycle. Except for Cycle 1 Day 1, these assessments may be performed up to 3 business days prior to the scheduled day.

Temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).

Blood pressure and pulse measurements should be assessed in a consistent manner throughout the study.

8.3.5 Clinical Safety Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1-1) for the timing and frequency.

The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant’s condition.

- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Table 1-1).
- Laboratory assessments will be performed at the laboratory affiliated with the study center.

- If laboratory values from laboratory tests not specified in the protocol and performed at the institution's local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the source document.
- Laboratory abnormalities that are considered by the Investigator to be clinically significant for a particular patient during Screening and before Study Drug administration are to be reported as part of the patient's medical history and as an AE after initiation of Study Drug, where the finding represents a change from Baseline.

8.3.6 Pregnancy Testing

- Serum or urine samples for beta-human chorionic gonadotropin pregnancy testing are to be collected from WOCBP during Screening, within 2 weeks before the first scheduled study therapy dose on Cycle 1 Day 1. Pregnancy testing is to be performed in closer proximity to Cycle 1 Day 1 as required by local/institutional regulations.
- Screening pregnancy test results must be reviewed and determined to be negative before administration of the first study therapy dose on Cycle 1 Day 1.
- Pregnancy testing is to be repeated during the study at any time pregnancy is suspected.
- All WOCBP will also have a pregnancy test at the EOT visit.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs considered related to the Study Drug or the study, or that caused the participant to discontinue the Study Drug (see Section 7). This includes events reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legal representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after the last dose of Study Drug as specified in the SoA (Table 1-1).

Any clinically significant medical conditions observed after a participant signs the ICF, e.g., during screening are to be assessed by the investigator and recorded as medical history if present prior to signing the ICF and unchanged. Any new or worsening conditions noted following the ICF signature date should be recorded as an AE.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in Appendix 3. The Investigator will submit any updated SAE data within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the Study Drug or study participation, the Investigator must promptly notify the Sponsor or designee.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts through the 30-day Safety follow-up visit. Where possible, SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, see Appendix 3) by the Investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a Study Drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a Study Drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs that occur during the study, and all SAEs occurring up to 30 days after receiving the last dose of Study Drug, whether considered to be associated with the Study Drug or not, must be reported within 24 hours to the Parexel Safety Contact using the numbers in the List of Study Personnel.

Investigator safety reports must be prepared and submitted for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy. Submission of blinded periodic line listings to Investigators will also be performed according to local requirements.

8.4.5 Pregnancy

Details of all pregnancies in female participants and partners of male participants will be collected after the start of Study Drug and until 30 days after the last Study Drug dose.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours. Inspirna Clinical Safety and/or its collaborating Clinical Research Organization (CRO) will then forward the Exposure In Utero form to the Investigator for completion.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

The Investigator will follow the patient/ patient's partner until completion of the pregnancy and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

Abnormal pregnancy outcomes (e.g., maternal serious complications, therapeutic abortion, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

The participant/pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant partner and the neonate, and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the Study Drug by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue Study Drug and be withdrawn from the study. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with metastatic CRC and can be serious/life-threatening:

- Clinical and/or Radiographic Disease Progression

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of AEs/SAEs even though the event may meet the definition of a SAE. These DREs will be monitored by the DMC. See Section10.1.4.1.

NOTE: However, if the following condition applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The Investigator considers that there is a reasonable possibility that the event was related to Study Drug.

8.5 Pharmacokinetics

Collection of blood samples for plasma concentrations of ompenaclid will be performed prior to the morning dose of Study Drug on Day 15 of Cycles 1 and 2.

Detailed instructions for collecting, processing, storing, and shipping the PK samples are provided in the Laboratory Manual.

8.6 Pharmacodynamics

There are no pharmacodynamics assessments performed in this study.

8.7 Genetics

Genetics are not evaluated as an outcome in this study.

8.8 Biomarkers

Tumor tissue (a minimum of 5 and up to 15 unstained formalin-fixed paraffin-embedded slides, or formalin-fixed paraffin-embedded block) obtained from an archival tissue sample is requested to be submitted to the central lab as soon as feasible during the study. If both a primary tumor and metastatic biopsy are available, both may be submitted. The tumor tissue will be evaluated for CKB immunohistochemistry expression and may be evaluated for other non-genetic biomarkers (e.g., markers related to the phosphocreatine transport pathway).

Tissue samples collected at the respective treatment sites will be immediately shipped to the designated laboratory for analysis. Where archival tissue blocks are submitted, the central lab will prepare slides as soon as possible and the remaining block will be returned to the study center.

8.9 Immunogenicity Assessments

No immunogenicity evaluations will be performed in this study.

9 Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to the first DMC review of the study data, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Exploratory analyses will be described in the SAP.

9.1 Statistical Hypotheses

Primary Objective

The primary objective is to demonstrate that ompenaclid is superior to placebo in achieving CR or PR (determined as ORR). The null hypothesis is that there is no difference in ORR between ompenaclid and placebo, while the alternative hypothesis is that there is a difference in ORR between treatment groups, with ompenaclid having a higher ORR. This hypothesis will be tested using a stratified analysis of the difference of two proportions as described in Section 9.3.2.2.

Key Secondary Objective

The key secondary objective is to demonstrate that ompenaclid is superior to placebo in PFS time. This hypothesis will be tested using a stratified log-rank test as described in Section 9.3.3.1.

Additional Secondary Objectives

The additional secondary objectives are to demonstrate that ompenaclid is superior to placebo for OS, DoR, and DCR. These hypotheses will be tested using a stratified analyses described in Sections 9.3.3.2, 9.3.3.3, and 9.3.3.4.

9.1.1 Multiplicity Adjustment

Given that this is a Phase 2 proof-of-concept study, there will be no attempt to preserve the overall type 1 error rate. All statistical tests will be performed at a one-sided significance level of 5%.

9.2 Analysis Sets

Efficacy analyses will be performed in the intention-to-treat (ITT) population, consisting of all randomized patients. Patients will be allocated to treatment groups as randomized, and not by actual Study Drug received.

Safety analyses will be performed in the safety population, consisting of all randomized patients who received any quantity of Study Drug, with patients grouped by actual treatment received.

9.3 Statistical Analyses

9.3.1 General Considerations

Baseline is defined as the last measurement for a variable prior to the first dose of Study Drug. Missing data will not be imputed. All data collected on the eCRF will be listed. Routine data listing or tabulation review during the study conduct will be performed in a blinded fashion to identify missing data, anomalies, outliers, etc.

A complete description of data handling rules and planned statistical analyses will be detailed in the SAP. The SAP will supersede the protocol in the event of any difference between the two documents in the plans for data analysis.

Further details of the analyses described below, including censoring conventions for the analysis of time-to event outcomes (PFS, OS, and DoR), will be provided in the SAP.

9.3.2 Primary Endpoint Analysis

9.3.2.1 Definition of Endpoint

The primary efficacy endpoint of this study is ORR, defined as the proportion of patients achieving a best response of CR or PR per the investigators using RECIST version 1.1.

9.3.2.2 Main Analytical Approach

Comparison of ORR between treatment groups will be by a one-sided Mantel-Haenszel (MH) test of the difference in two proportions stratified by the randomization stratification factor using a type I error rate of 5%. The estimated MH ORR difference will be summarized along with the two-sided 90% confidence interval using MH stratum weights and Sato variance estimator.

9.3.3 Secondary Endpoints Analysis

9.3.3.1 Progression-free Survival (Key Secondary Endpoint)

The key secondary efficacy endpoint of this study is PFS, defined as the time from the date of randomization to the date of objectively determined PD per the investigators using RECIST version 1.1 or death from any cause, whichever occurs first. If a given patient is alive at the end of the follow-up period or is lost to follow-up without evidence of PD, PFS will be censored at the date of their last objective progression-free assessment. If no baseline or post-baseline radiologic assessment is available, the patient will be censored at the date of randomization. For patients who receive subsequent anticancer therapy prior to PD or death, PFS will be censored at the date of the last objective progression-free assessment prior to the date of subsequent therapy. Additional details regarding the definition of PFS will be provided in the SAP.

Comparison of PFS between the treatment groups will be by a stratified log-rank test. A treatment hazard ratio (HR) and associated two-sided 90% confidence interval will be estimated from a stratified Cox proportional hazards model. The distributions of PFS for each treatment group will be estimated by Kaplan-Meier methods. The percentage of patients in each treatment group without a PFS event at selected landmarks after randomization (e.g., 24 weeks) based on Kaplan-Meier estimates will also be summarized.

9.3.3.2 Overall Survival

OS is defined as the time from the date of randomization to the date of death from any cause. If a given patient is alive at the end of the follow-up period or is lost to follow-up, OS data will be censored on the last date the patient is known to be alive. Comparison of OS between treatment groups will follow the methods used for PFS.

9.3.3.3 Duration of Response

DoR is defined as the date of objectively determined PR or CR (whichever status is recorded first) to the date of objectively determined PD per the investigators using RECIST version 1.1 or death from any cause, whichever occurs first. Comparison of DoR between treatment groups will follow the methods used for PFS.

9.3.3.4 Disease Control Rate

DCR is defined as the proportion of patients achieving a best response of CR, PR, or SD; SD must be documented at least 6 weeks after randomization. Comparison of DCR between treatment groups will follow the methods used for ORR.

9.3.4 Safety and Population Analyses

All safety data will be summarized by treatment group. No inferential statistics will be performed for safety variables. Safety analyses in addition to those described in the following subsections may be determined at any time without prejudice, to clearly enumerate the rates of toxicities and to further define the safety profile of the Study Drug in combination with FOLFIRI + bevacizumab.

9.3.4.1 Adverse Events

AEs will be considered treatment-emergent (TEAE) if they start on or after the time of the first dose of Study Drug and up to 30 days after the last dose of Study Drug. AEs will be coded using MedDRA Version 26.0 (or higher) and summarized by System Organ Class (SOC) and preferred term (PT). The severity of AEs will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 (or higher) grade. Non-treatment-emergent AEs will be included in the patient listings and flagged as such but will not be included in the summary tables. Adverse events with missing start and/or end dates and/or times will be handled as described in the SAP. Where an AE date is partial or missing, and it is unclear whether the AE is treatment-emergent, the AE will be assumed to be treatment-emergent.

The number and percentage of patients who experience TEAEs will be summarized overall by SOC and PT and will also be summarized based on severity and causality.

Descriptive analysis of AEs will include incidence of TEAEs grouped by:

- SOC and PT
- SOC, PT, and severity

- SOC, PT, and causality
- SOC and PT leading to discontinuation from the study
- SOC and PT for events with CTCAE Grade ≥ 3
- SOC and PT leading to death

Individual listings of all AEs will also be provided.

9.3.4.2 Laboratory Parameters

Laboratory results (hematology, serum chemistry, coagulation parameters and urinalysis) will be classified according to NCI-CTCAE, Version 5.0. Laboratory results not corresponding to an NCI-CTCAE term will not be graded. Laboratory data will be listed, and abnormal results will be flagged. Planned analyses of laboratory data will be described in the SAP.

9.3.4.3 Vital Signs

Planned analyses of clinically significant changes in vital sign parameters (as defined in the SAP), including systolic and diastolic blood pressure, heart rate, and body weight will be described in the SAP. Any clinically significant abnormal values will be captured as AEs. Vital signs data will be listed.

9.3.4.4 ECOG Performance Status

ECOG performance status will be summarized by cycle and worst status overall; ECOG performance status will be presented in data listing format.

9.3.4.5 Physical Examination

The analysis of physical examination will focus on patients who develop abnormalities post-baseline or whose evaluations worsen after Baseline. The results of abnormal physical examinations will be listed as adverse events.

9.3.4.6 Electrocardiograms

The proportions of patients with treatment-emergent clinically significant ECG abnormalities (as defined in the SAP) will be tabulated, and changes in ECG findings will be presented in data listing format. Categorical analyses of QTc interval data will be performed per the SAP.

9.3.5 Steady State Pharmacokinetics Analysis

The steady state pharmacokinetics of ompenaclid will be analyzed from the samples collected on Day 15 in Cycles 1 and 2. Concentration data will be summarized descriptively for each scheduled sampling time point.

9.3.6 Population Data

Disposition, including primary reason for withdrawal from the study, will be summarized by treatment group for the ITT population. Demographic information and patient characteristics including, but not limited to, sex, age, baseline ECOG performance score, prior therapies, and medical and cancer histories will also be summarized by treatment group for the ITT population.

Medications will be coded using the World Health Organization Drug Dictionary and listed by subject. A summary of concomitant medications by treatment group and medication class will also be tabulated.

Major Protocol deviations will be listed and summarized by treatment group and category.

9.3.7 Other Analyses

Subgroup analyses of the primary and secondary endpoints may be made to assess consistency of the investigational intervention effect (ORR, PFS, OS, DoR, and DCR) across subgroups, for example:

- Prior bevacizumab or EMA-approved biosimilar treatment (yes vs. no)
- Sex
- Time from initiation of first-line treatment to PD (< 6 months, 6 to 12 months, >12 months)

Additional subgroups may be specified in the SAP.

9.4 Interim Analysis

The DMC will conduct unblinded interim safety analyses approximately every 6 months following randomization of the first patient. The DMC will also conduct unblinded interim efficacy analyses, the timing and scope of which will be outlined in the DMC charter.

The DMC charter will describe the planned interim analyses in greater detail.

9.5 Sample Size Determination

The sample size calculation is based on a one-sided Z-test (unpooled variance) of the difference in two proportions for comparing ORR between the treatment groups, with the following assumptions:

- ORR = 35% and 10% for the ompenaclid and placebo groups, respectively.
- One-sided type 1 error = 5%

- Power ≥ 80%

Under these assumptions, 70 patients will be randomized 1:1 into the treatment groups. Additional patients may be randomized into the study in order to ensure at least 40 disease progression events are observed for evaluation of the key secondary objective of the study. This number of events will provide ≥70% power to detect a HR of 0.50 with one-sided type 1 error = 5%.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.2 Financial Disclosure

The Investigators and subinvestigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator and subinvestigators must provide to the Sponsor a commitment to update promptly this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the Sponsor nor the CRO is financially responsible for further testing/treatment of any medical condition, which may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

10.1.3 Informed Consent Process

The Investigator or the Investigator's representative at each center will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. The potential participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. All patient personal data will be processed in accordance with the General Data Protection Regulatory (No 2016/679 from 25May2018).

The Sponsor will implement technical and organizational measures to ensure the security and privacy of any personal data that the Sponsor will collect, receive, process, disclose or store throughout the duration of the study, including the execution of Standard Contractual Clauses to ensure the valid transfer of personal data outside the EU. Two other key components of the technical and organizational measures include a Privacy Breach Response Plan that will guide the identification, risk assessment, containment, notification and remediation of a breach. The second component to comply with Data Protection requirements includes the development of a Data Protection Impact Assessment that identifies the privacy risks, including security breaches, and the mitigations that will be implemented to manage these risks.

10.1.4.1 Data Monitoring Committee

Interim analyses of safety and efficacy will be monitored by the DMC, which will be governed by the DMC charter.

10.1.5 Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

Within the EU, the Sponsor will submit independent Annual Safety Reports for all study interventions in this clinical study.

10.1.6 Data Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor via a paper record, e.g., hard-copy SAE report. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Guidance on completion of CRFs will be provided in the electronic data capture system.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Agency inspections and provide direct access to source documents.

Monitoring details describing strategies, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

The Investigator will retain the records of the study for 2 years following the last date that a marketing application for ompenaclid is approved in any ICH region, or if marketing approval is not obtained, for 2 years after the European Medicines Evaluation Agency (EMEA) application for ompenaclid has been closed in EMEA region or until there are no pending contemplated marketing applications in an ICH region. These documents should be retained for a longer period; however, if required by the application regulatory requirements or by an agreemnet with the Sponsor. The Sponsor will notify Investigators when study records retention is no longer required. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant signing first informed consent in line with first subject first visit and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further Study Drug development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

The results of this multicenter study may be published or presented at scientific meetings by the Sponsor. Other publication policies will be described in each site’s Clinical Trial Agreement.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by the Sponsor.

10.1.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured for personal injury caused by the Study Drug or by properly performed medical steps taken in the course of the study in accordance with the protocol.

10.1.12 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out

giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor, and Parexel if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The routine safety tests detailed in Table 10-1 will be performed by the investigator's local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants based on laboratory parameters are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Urea Potassium Creatinine Sodium Glucose (fasting) Calcium	AST/SGOT Total and direct bilirubin ALT/SGPT Total protein Alkaline phosphatase [1]
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)	
Pregnancy testing	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential) at timepoints detailed in the SoA (Table 1-1)[2]	
Other tests	CKB analysis of tumor samples	

NOTES:
1. If alkaline phosphatase is elevated, consider fractionating.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

ALT= alanine aminotransferase; AST= aspartate aminotransferase; hCG= human chorionic gonadotropin; IEC= independent ethics committee; INR= international normalized ration; IRB= institutional review board; RBC= red blood cell; SGOT= serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase; WBC= white blood cell.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease, or more severe than expected for the participant's condition).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Lack of efficacy or *failure of expected pharmacological action* per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE/SAE Definition

Clinical Disease progression. Similarly, hospice admission or hospitalization for respite care related to disease progression are not to be reported as SAEs.

Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is an AE that:

a. **Results in death**

b. **Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations**

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the safety team in lieu of completion of the required EDC or paper back-up SAE form.

There may be instances when copies of medical records for certain cases are requested by the safety team. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor safety team.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity (Grade) for each AE and SAE reported during the study according to NCI CTCAE Criteria v5.0.

For events with no corresponding CTCAE Criteria intensity should be assigned it to one of the following categories:

Grade 1 (Mild): An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.

Grade 2 (Moderate): An event that causes sufficient discomfort to interfere with normal everyday activities.

Grade 3 (Severe): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Grade 4 (Life-threatening): An event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Grade 5 (Death)

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship simply cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the electronic data collection tool.**

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following "binary" decision choice will be used by the Investigator to describe the initial causality assessment:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The Investigator may be requested by the Sponsor to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed form.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAE

SAE Reporting via Electronic Data Collection Tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours of awareness.

The site will enter the SAE data into the electronic system as soon as it becomes available.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/Parexel will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table).

Contacts for SAE reporting can be found below.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSAR reporting will be in adherence to requirements of EU pharmacovigilance legislation, Clinical Trial Regulation (CTR) legislation and guidance. EU CTR 536/2014; CT-3 and all other applicable local regulations.

Serious Adverse Events Contact Details

To report an SAE when the EDC is down, please refer to the applicable study manual or eCRF guidance for SAE reporting instructions.

If the EDC is down, SAEs should be reported to the following phone number:

France (Paris): +33 1 44 90 32 90

For back-up paper reporting, SAEs shall be reported to RGX202002@ Parexel.com.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal

2. Premenopausal female with either:

   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the subject's medical record for the study.

10.4.2 Acceptable Methods of Contraception

For WOCBP who participate in the study, the following methods of contraception, if used properly and used for the duration of the study, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, implantable hormonal contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the subject's current practice. Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods, are not an acceptable form of contraception for this study.

These methods of contraception also apply to female partners of male subjects.

The Investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study. This will be documented in the subject's source documentation/medical record.

11 References

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Investigator Agreement Page

Declaration of the Investigator

Title: A randomized Phase 2 Study of ompenaclid versus placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated *RAS* mutant advanced or metastatic colorectal cancer

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic CRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number