1.0 Title Page

Clinical Study Protocol M14-217

Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer

Incorporating Amendments 1 and 2

AbbVie Investigational Product:	Veliparib (ABT-888)
Date:	16 July 2015
Development Phase:	2
Study Design:	Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer
EudraCT Number:	2014-002866-65
Investigator:	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie Inc.*

[redacted]

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Update contact information for the AbbVie Study Designated Physician.

  Rationale: *Change in Study Designated Physician assigned to the trial.*
- Provide timing windows around the infusion duration of fluorouracil, irinotecan, leucovorin and bevacizumab.

  Rationale: *To allow reasonable flexibility in the administration of protocol therapy.*
- Section 1.2, Synopsis, add bevacizumab as a reference therapy in the table.

  Rationale: *Bevacizumab was missing in the previous version of the protocol.*
- Section 1.2, Synopsis, and Section 5.2.2, Exclusion Criteria, clarify that Exclusion Criterion 3 pertains to neoadjuvant chemotherapy in addition to adjuvant therapy and change "prior to colorectal cancer recurrence" to "prior to C1D–2."

  Rationale: *To remove ambiguity around the timing of treatment and to increase uniformity of elapsed time between prior treatment and study entry, as time to recurrence could be subjective/unknown in many cases.*
- Section 1.2, Synopsis, and Section 5.2.2, Exclusion Criteria, add a definition to symptomatic congestive heart failure.

  Rationale: *Clarify what constitutes as clinically significant using a well-established classifier.*
- Section 3.8, Clinical Experience, correct inaccurate adverse event frequencies from Study M10-977, Phase 1 dose escalation study.

  Rationale: *Incorrect information was included in the previous version of the protocol.*
- Section 5.1, Overall Study Design and Plan: Description, update Figure 1 to reflect that subjects will receive **either** fluorouracil or saline bolus and illustrate that the 46-hour 5-FU infusion will continue into Day 3.

  Rationale: *The option of a saline bolus was missing from the figure.*

- Section 5.1, Overall Study Design and Plan: Description, and Section 5.4.5, Timing and Collection of Survival and Post-Treatment Cancer Information, clarify that the survival information and post-treatment cancer information will be collected beginning 4 weeks after the last clinical assessment.

  Rationale: *The previous version of the protocol noted "after the last study visit" which could be interpreted as the Final Visit or the Follow-up Visit.*

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, remove physical exam requirement at C1D1.

  Rationale: *From a medical perspective, the physical exam at C1D–2 is sufficient for this population.*

- Section 5.3.1.1, Study Procedures, clarify that RAS, BRAF and MSI status only need to be captured in Medical History if known.

  Rationale: *Not all sites perform these tests as part of their standard of care.*

- Section 5.3.1.1, Study Procedures, Table 7, Clinical Laboratory Tests, update clinical chemistry terminology.

  Rationale: *To standardize medical terminology for clinical labs and comply with the current protocol template.*

- Section 5.3.2.1, Blood Samples for Pharmacokinetic Analysis, update the information that is to be captured.

  Rationale: *Clarify that the date and time of sample collection, the date and time of the veliparib/placebo dose on PK sampling days and the date and time of the two doses of veliparib/placebo prior to PK sampling on C2D1 and C3D1 will be captured.*

- Section 5.3.2.2, Measurement Methods, revise "non-GLP" to "non-validated."

  Rationale: *To clarify the meaning of "non-GLP."*

- Section 5.3.2.3, Blood Samples for Pharmacogenetic Analysis, revise the label for the pharmacogenetic sample collection tube from "PG-DNA" to "PG-DNA blood."

  Rationale: *To comply with the current protocol template.*

- Section 5.3.7, Pharmacodynamic Variables, and Section 5.4, Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits, update storage and retention language for the pharmacodynamics samples.

Rationale: *To ensure consistency with the template language and align with the informed consent.*

- Section 5.4, Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits, update language regarding consent withdrawal and the pharmacodynamic samples.

  Rationale: *To ensure consistency with the template language.*

- Section 5.5.1, Protocol Therapy Administered, specify that sites can use their own method for calculating body surface area (BSA), and dose re-calculations must be made if a subject's weight increases or decreases by more than 10%.

  Rationale: *To allow reasonable flexibility in the administration of protocol therapy.*

- Section 5.5.1, Protocol Therapy Administered, update protocol therapy administration to allow for sequential infusion of irinotecan followed by leucovorin.

  Rationale: *To address equipment shortages in European countries that preclude concurrent administration.*

- Section 5.5.9, Blinding, update language regarding unblinded AbbVie study personnel.

  Rationale: *To clarify the role of unblinded internal study team members.*

- Section 6.7, Adverse Event Reporting, update information regarding reporting SAEs if the site does not have access to EDC or the system is not operable and update the 24-hour AbbVie Medical Escalation Hotline information.

  Rationale: *To comply with the current protocol template.*

- Section 7.0, Protocol Deviations, update language regarding intentional/prospective deviations from the protocol.

  Rationale: *To comply with the current protocol template.*

- Section 8.1.7, Interim Analysis, update interim analysis plan.

  Rationale: *To clarify timing, scope and rationale of the two planned interim analyses.*

- Appendix I, Toxicity Management Guidelines for Protocol Therapy, update language regarding dose modifications and unresolved toxicity.

Rationale: *To clarify when dose modifications should be made with respect to timing of unresolved toxicity.*

- Additional minor corrections and clarifications.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix J.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-217
Name of Study Drug: Veliparib or ABT-888	**Phase of Development:** 2
Name of Active Ingredient: Not applicable	**Date of Protocol Synopsis:** 16 July 2015
Protocol Title: Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer	
Objectives: The primary objectives of the study are to assess whether the addition of oral veliparib to FOLFIRI will improve progression-free survival (PFS) in subjects with metastatic colorectal cancer (mCRC). The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), safety, and tolerability. The tertiary objectives of the study are to assess duration of overall response (DOR) and performance status.	
Investigators: Multicenter	
Study Sites: Approximately 60	
Study Population: Subjects with metastatic adenocarcinoma of the colon or rectum who have not received prior chemotherapy for their mCRC. Subjects must have at least one unresectable lesion that is measurable per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.	
Number of Subjects to be Enrolled: Approximately 120	
Methodology: This is a blinded, randomized, placebo-controlled study to evaluate the efficacy and tolerability of veliparib in combination with FOLFIRI ± bevacizumab (bevacizumab will be administered at the discretion of the Investigator) in previously untreated metastatic adenocarcinoma of the colon or rectum. Subjects will be randomized to one of two protocol therapy groups as follows: a. Veliparib plus FOLFIRI ± bevacizumab b. Placebo plus FOLFIRI ± bevacizumab Note that for the purposes of this protocol, FOLFIRI is used to describe both the standard regimen containing a 5-FU bolus that will be administered to subjects randomized to the placebo arm, and a modified regimen with a saline bolus that will be administered to subjects randomized to the veliparib arm. Randomization will be conducted to ensure that at least 60 subjects are enrolled in both the "planned bevacizumab use" group and "no planned bevacizumab use" group for a total of ~120 subjects.	

Methodology (Continued):

Protocol Therapy

For the purposes of this study, protocol therapy will be defined as veliparib/placebo in combination with FOLFIRI ± bevacizumab at the following dose levels. One cycle of protocol therapy consists of 14 days, defined from Day –2 through Day 12. Dosing of oral veliparib/placebo will begin 2 days prior to the start of FOLFIRI and will continue twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) may be administered intravenously immediately preceding FOLFIRI. Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle. FOLFIRI is only to be given after veliparib/placebo dosing on cycle Day –2 and Day –1 are confirmed. Subjects should continue to follow the dosing schedule for protocol therapy until disease progression or other criteria for protocol discontinuation are met.

Study Visits and Study Discontinuation Criteria

Screening procedures and baseline radiographic tumor assessments will be performed within 28 days prior to the first dose of veliparib/placebo on C1D–2. Study visits will be conducted on Day 1 and Day 8 of the first and second cycle, then on Day 1 of each subsequent cycle.

Post-baseline tumor assessment will be conducted every 8 weeks from C1D1 (prior to the start of a new cycle) until radiographic progression.

Subjects with controlled disease (complete response [CR], partial response [PR], or stable disease [SD]) and with tolerable side effects may continue to receive protocol therapy until disease progression.

When the Investigator has determined that subject should discontinue protocol therapy, a Final Visit will be conducted. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of protocol therapy.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- ≥ 18 years of age;
- Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum;
- At least 1 unresectable lesion on a CT scan that is measurable as defined by RECIST, Version 1.1;
- ECOG performance score of 0 or 1;
- Adequate hematologic, renal and hepatic function as follows:
  - Bone marrow: Absolute Neutrophil count (ANC) ≥ 1,500/µL; Platelets ≥ 100,000/mm^3; (independent of platelet transfusions within 3 months prior to starting protocol therapy); Hemoglobin ≥ 9.0 g/dL;
  - Renal function: Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 50 mL/min;
  - Hepatic function and enzymes: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN) of institution's normal range. Subjects with liver metastases may have an AST and ALT of ≤ 5.0 × ULN;

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Bilirubin: ≤ 1.5 × the ULN of institution's normal range.

- If female, subject must be postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing at least one of the following methods of birth control until 90 days after the last dose of protocol therapy:
  - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable;
  - Vasectomized partner(s);
  - Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior C1D–2 (if the subject is currently using a hormonal contraceptive, she should also use a barrier method during the study and for 1 month after protocol therapy completion);
  - Intrauterine device (IUD);
  - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams).
- If male, subject must be surgically sterile or practicing at least one of the following methods of contraception, from the initial protocol therapy administration until 90 days after the last dose of protocol therapy:
  - Partner(s) using IUD;
  - Partner(s) using hormonal contraceptives (oral, vaginal, parenteral or transdermal);
  - Subject and/or partner(s) using double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams);
  - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable.
- Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

For Subjects Receiving Bevacizumab:

- Blood pressure must be well controlled (< 160/90 mm Hg) on a stable regimen of anti-hypertensive therapy for at least 2 weeks.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

- Prior anti-cancer treatment for metastatic colorectal cancer;
- Prior exposure to PARP inhibitors;
- The last course of adjuvant or neoadjuvant chemotherapy must have ended > 12 months prior to C1D–2;
- Known Gilbert's Syndrome;
- Prior radiotherapy to greater than 25% of bone marrow;
- Prior radiotherapy ≤ 4 weeks of C1D–2;
- Any type of major surgery ≤ 4 weeks of C1D–2;
- Previous or concurrent malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the subject has been disease-free for 3 years;
- Known hypersensitivity to irinotecan, 5-FU or leucovorin;
- Clinically significant and uncontrolled major medical condition(s) including but not limited to:
  - Uncontrolled nausea/vomiting/diarrhea;
  - Active uncontrolled infection;
  - Symptomatic congestive heart failure (NYHA Class ≥ II);
  - Unstable angina pectoris or cardiac arrhythmia;
  - Psychiatric illness/social situation that would limit compliance with study requirements.
- Predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline pattern of > 3 watery of soft stools daily. Subjects with an ileostomy or colostomy may enter the study at the discretion of the Investigator;
- Subject is pregnant or lactating;
- Subject who requires parenteral nutrition, tube feeding or has evidence of partial bowel obstruction or perforation within 28 days prior to C1D–2;
- Any medical condition, which in the opinion of the study Investigator, places the subject at an unacceptably high risk for toxicities.
- Subject has received an investigational drug within the 28 days prior to Screening.
- Any subjects will be excluded if prohibited from participation according to local laws or regulations.

For Subjects Receiving Bevacizumab:

- Prior treatment with bevacizumab;
- Known central nervous system metastases;
- Significant history of bleeding events or GI perforation;
  - Subjects with a history of significant bleeding episodes (e.g., hemoptysis, upper or lower GI bleeding) within 6 months of C1D–2 are not eligible unless the source of bleeding has been resected;
  - Subjects with a history of GI perforation within 12 months of C1D–2 are not eligible;
- Serious or non-healing wound, ulcer or bone fracture;
- History of venous or arterial thromboembolism within 2 months of enrollment;
- Known hypersensitivity to recombinant or murine antibodies.

Investigational Product:	Veliparib (ABT-888) or Placebo
Dose:	200 mg twice a day (BID), Day –2 through Day 5 of each 14-day cycle
Mode of Administration:	Oral
Reference Therapy:	Irinotecan
Dose:	180 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	Intravenous (IV) over 90 minutes ± 30 minutes
Reference Therapy:	Leucovorin (Folinic Acid)
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 90 minutes ± 30 minutes
Reference Therapy:	Fluorouracil (5-FU) bolus or saline bolus
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV up to 15 minutes
Reference Therapy:	Fluorouracil (5-FU) infusion
Dose:	2400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 46 hours ± 4 hours
Reference Therapy:	Bevacizumab (at the Investigator's discretion)
Dose:	5 mg/kg
Mode of Administration:	IV immediately preceding FOLFIRI
Duration of Treatment: Subjects with controlled disease (CR, PR, or SD per RECIST, Version 1.1) and with tolerable side effects may continue to receive protocol therapy until disease progression.	
Pharmacokinetic: Blood samples will be collected at designated time points throughout the study.	
Pharmacodynamic: Research to find biomarkers that may serve as surrogates for clinical endpoints in future veliparib studies or that may be predictive of veliparib activity will be conducted. Serum, plasma, blood and tissue samples will be collected at designated time points throughout the study.	
Statistical Methods: For all statistical analyses, *P* values will be provided. The date of randomization (enrollment) is defined as the date that the Interactive Response Technology (IRT) system issues a randomization number. **Sample Size:** A minimum of 70 PFS events was chosen to provide adequate precision in the hazard ratio estimate. Assuming median PFS time of 9.4 months in the FOLFIRI ± bevacizumab arm and 15.7 months in the veliparib plus FOLFIRI ± bevacizumab arm, based on a minimum of 70 PFS events, the expected 95% confidence interval for the estimated hazard ratio would be approximately 0.37 to 0.96. A total of 120 subjects will be enrolled into the study. Assuming a total enrollment period of 12 months, it is anticipated that the study will complete by end of the 22nd month if the true median times for each treatment arm are as assumed above.	

Statistical Methods (Continued):

Efficacy:

Primary

Progression-Free Survival (PFS): will be defined as the number of days from the date the subject is randomized to the date the subject experiences a disease progression event or to the date of death if disease progression is not reached. The progression-free survival distribution will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using a log-rank test stratified by the planned bevacizumab use. A two-sided, stratified log-rank test *P* value will be provided. Median PFS time will be estimated and a 95% confidence interval for the median PFS time will be presented for each treatment group. A hazard ratio estimate and a 95% confidence interval will be obtained from a proportional hazards regression model.

Secondary

Overall Survival (OS): Time to death for a given subject will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive. The distribution of overall survival will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using a log-rank test stratified by the planned bevacizumab use. Median OS time will be estimated and a 95% confidence interval for the median OS time will be presented for each treatment group. A hazard ratio estimate and a 95% confidence interval will be obtained from a proportional hazards regression model.

Objective Response Rate (ORR): (CR and PR) will be defined as the proportion of subjects with a complete or partial objective response based on RECIST, Version 1.1. The objective response rate will be estimated and compared between the two treatment groups using a Cochran-Mantel-Haenszel test, stratifying by the planned bevacizumab use. In addition, a 95% confidence interval will be constructed for the estimated proportions.

Safety:

Safety will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory data and vital signs. Subjects who are randomized but do not receive study drug (veliparib) or placebo will not be included in the analyses of safety. Safety analysis results will be presented by treatment group.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

5-FU	5-fluorouracil
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BID	Twice a Day
BUN	Blood Urea Nitrogen
C	Cycle
D	Day
CEA	Carcinoembryonic Antigen
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CYPs	Cytochrome P450s
DDI	Drug-drug Interactions
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid (DNA)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
FOLFIRI	Irinotecan, Fluorouracil, and Leucovorin chemotherapy regimen
FOLFOX	Oxaliplatin, Fluorouracil, and Leucovorin chemotherapy regimen
GI	Gastrointestinal

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IMC	Internal Monitoring Committee
IEC	Independent Ethics Committee
IIA	Investigator Information and Agreement
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
mCRC	Metastatic colorectal cancer
MMR	Mismatch-Repair
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PAR	Poly(ADP-ribose)
PARP	Poly(ADP-ribose)-polymerase
PD	Pharmacodynamic
PG	Pharmacogenetic
PFS	Progression-Free Survival
PK	Pharmacokinetic
POR	Proof of Receipt
PR	Partial Response
PT	Prothrombin Time
QTc	QT Interval Corrected for Heart Rate
RBC	Red Blood Cell

RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SD	Stable disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMZ	Temozolomide
ULN	Upper Limit of Normal
WBC	White Blood Cell

2.0 Table of Contents

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3.0 Introduction

3.1 Colorectal Cancer

Colorectal cancer is the third most common cancer in men and the second most common cancer in women with 746,000 and 614,000 cases respectively worldwide in 2012.[1] Metastatic colorectal cancer remains a largely incurable disease. The majority of patients faced with a diagnosis of metastatic colorectal cancer have either extensive liver disease or disease outside the liver, limiting their treatment options to chemotherapy. Current chemotherapy treatment options for these patients include fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-afilbercept, and regorafenib administered in various combinations or as single agents.[2] While the introduction of each of these regimens has resulted in incremental increases in patient survival, the 5-year survival rate for advanced colorectal cancer remains at only ~6%.[3]

3.2 FOLFIRI

Fluorouracil (5-FU) is commonly administered with leucovorin (folinic acid), which modulates 5-FU activity. Irinotecan is active in advanced colorectal cancer and was first approved by the FDA for patients with disease refractory to 5-FU/leucovorin. Initial approval was based on a response rate of about 15% and subsequently confirmed with a randomized study demonstrating improved survival for patients refractory to 5-FU who were treated with irinotecan compared to best supportive care.[4] Two combinations of irinotecan/5-FU/leucovorin were compared to 5-FU/leucovorin regimens, one with bolus 5-FU/leucovorin and another with continuous infusion 5-FU (FOLFIRI).[5,6] In both studies, the irinotecan-containing combinations conferred a survival advantage, leading to the indication of these regimens as standard front-line therapy for patients with metastatic colorectal cancer (mCRC). The bolus 5-FU/leucovorin and irinotecan combination was once favored in the US, although it appears to be more toxic than the FOLFIRI regimen, and the general consensus is that FOLFIRI merits further testing in the US. In Europe, FOLFOX and FOLFIRI have been compared to each other, used sequentially, in the management of patients with advanced colorectal cancer, and there does not appear to be

a significant difference in outcome based on the sequence of administration, although the toxicity profiles are dissimilar.[7] The treatments have not been compared head-to-head in the US.

3.3 Bevacizumab

Bevacizumab (Avastin) is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody that has been clinically evaluated both as a single agent and in combination with cytotoxic chemotherapy in multiple metastatic solid tumor types. It is approved for use in the first-line setting for advanced colorectal cancer in combination with fluorouracil-based chemotherapy. In a study comparing irinotecan/5-FU/leucovorin with irinotecan/5-FU/leucovorin plus bevacizumab in first-line mCRC, a survival advantage of more than four months was observed in bevacizumab-treated patients.[8] In the BICC-C Phase 3 study of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line metastatic CRC by Fuchs and colleagues, PFS and OS were improved in bevacizumab combination versus respective chemotherapy only arms. For FOLFIRI, PFS improved from 7.6 to 11.2 months and OS from 23.1 to 28 months with the addition of bevacizumab.[9] Bevacizumab does not appear to alter the toxicity profile of chemotherapy, although hypertension and proteinuria are commonly seen. Approximately 3.4% of patients receiving bevacizumab suffer arterial thrombotic events. Although there have been modest improvements in PFS and OS as noted above, given the risks of adding bevacizumab to standard chemotherapy, there remain many countries where bevacizumab is not considered first-line SOC for mCRC.

3.4 Veliparib

Poly(ADP-ribose)-polymerase (PARP) 1 and 2 are nuclear enzymes that recognize deoxyribonucleic acid (DNA) damage and facilitate DNA repair.[10,11] Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP enzymes then poly(ADP-ribosyl)ate many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus, PARP inhibition will result in less efficient DNA repair following a cytotoxic insult.

DNA-damaging agents including cytotoxic chemotherapy and radiation therapy, remain a mainstay of treatment for many patients with cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes that include large deletions, insertions, and unbalanced translocations of chromosomal material, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents.[12] Of these, deficiencies in mismatch repair or homologous recombination are associated with the largest number of malignancies. These deficiencies render cells more dependent on PARP for DNA repair, and hence more sensitive to PARP inhibition.[13] PARP enabled DNA repair may also compensate for the loss of other repair pathways. Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress.[14] PARP recognizes topoisomerase I cleavage complexes (Top1cc) that arise upon treatment with camptothecin and indenoisoquinoline anti-cancer compounds including Irinotecan. Activated PARP, in turn, is required for subsequent recruitment of Tyrosyl-DNA phosphodiesterase 1 (TDP1), a key repair enzyme for trapped Top1cc, and downstream base-excision repair (BER) proteins. Inhibition of PARP by veliparib prevents recruitment of these irinotecan damage repair enzymes, increases reliance on double-strand break generating nucleotide excision repair, and increases overall DNA-damage and cytotoxicity resulting from the chemotherapy.[15] Veliparib is a potent oral PARP inhibitor that delays the repair of DNA-damage induced by chemotherapeutic agents, including alkylating agents, platinums, radiation, and topoisomerase inhibitors. Nonclinical efficacy with veliparib in combination with these agents has been demonstrated across an array of tumor types, including melanoma, glioma, prostate, breast, and colon.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[14]

3.5 Rationale for Veliparib FOLFIRI Combination Therapy

Administration of veliparib in vitro or in vivo inhibits the formation of poly(ADP-ribose) (PAR) polymers. When veliparib and DNA-damaging cytotoxic agents are coadministered, veliparib inhibits the repair of DNA. In a variety of nonclinical tumor

models, including melanoma, breast, prostate, colon, and glioma, veliparib significantly enhanced the antitumor activity when dosed on a schedule that overlapped the administration of a DNA-damaging agent. Significant inhibition of tumor PAR levels at doses similar to those with antitumor effect was observed, which is consistent with veliparib potentiation of DNA-damaging agents being mediated through mechanistic inhibition of PARP. Specific to the context of damage induced by irinotecan, veliparib prevents PARP activation and subsequent recruitment of TDP1 and downstream BER enzymes required for repair without DNA double-strand break formation. Addition of veliparib to irinotecan thus increases reliance on double-strand break generating nucleotide excision repair, and increases overall DNA-damage and cytotoxicity resulting from the chemotherapy.[15] Therefore, patients receiving cytotoxic chemotherapy including irinotecan may benefit from the addition of a veliparib.

3.6 Veliparib Preclinical Toxicology

The toxicological profile of veliparib has been evaluated in nonclinical general toxicity studies that included single-dose (rats and mice), repeat-dose (duration of up to 6 months in rats and up to 9 months in dog), reproductive (embryofetal development in rat and rabbit), genetic (Ames, in vitro cytogenetics, in vivo micronucleus), phototoxicity (in vitro photosensitivity) and juvenile rat toxicity studies. Primary nonclinical findings included effects on the central nervous system (CNS) (convulsions, tremors), hematopoietic system (bone marrow depletion and resultant decreased circulating white and red blood cells), reproductive system (male germ cell depletion, female reproductive tract tissues degeneration), and lymphoid tissues (lymphocyte depletion), with lesser effects on the gastrointestinal tract (single-cell necrosis) and cardiovascular system (10% QTc interval prolongation). Convulsions and other CNS-related signs were considered exposure-dependent, and were generally self-limiting, ameliorated by dose reduction or cessation of dosing, or responsive to treatment. All other findings were dose dependent and reversible upon discontinuation of veliparib administration. Veliparib was also genotoxic (induced chromosomal aberrations in vitro and increased micronuclei formation in vivo) and was toxic to the developing fetus (increases in the incidence of

fetal external/visceral/skeletal malformations/variations) in rats and rabbits. Veliparib demonstrated no phototoxic potential in the photosensitivity assay. With the exception of CNS and cardiovascular effects, the toxicity of veliparib is generally consistent with the pharmacology of the compound.

3.7 Pharmacokinetics and Pharmacodynamics

A detailed discussion of the veliparib preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[14]

3.8 Clinical Experience

Veliparib has been investigated as a single agent and in combination with various DNA-damaging agents in subjects with different cancer types. Overall, approximately 1,255 cancer subjects have been exposed to veliparib in AbbVie sponsored studies as of 24 March 2014. Additionally, in the Cancer Therapy Evaluation Program (CTEP) sponsored studies of veliparib, approximately 1,687 adult subjects and 44 pediatric subjects have been exposed to veliparib as of 31 March 2014.

AbbVie sponsored studies included the evaluation of veliparib in combination with temozolomide, whole brain radiation therapy, concurrent radiation therapy and temozolomide, carboplatin and gemcitabine, carboplatin and paclitaxel, and FOLFIRI in Phase 1 and Phase 2 clinical studies. The main toxicities associated with veliparib to date are mechanism based and are not clearly distinguished from those expected of the base regimens with which veliparib is combined. Hematological toxicities, such as thrombocytopenia and neutropenia, and gastrointestinal (GI) disturbances such as nausea and vomiting, are the main toxicities observed to date.

Study M10-977 was a Phase 1, open-label dose escalation study evaluating the safety and tolerability of veliparib in combination with modified bimonthly FOLFIRI.[16] As of 14 March 2014, 96 subjects had been enrolled, enrollment was complete, and 6 patients remained on study. Although combining veliparib with standard FOLFIRI including a 5-FU bolus (400 mg/m^2) was not tolerated, veliparib was dose escalated from 10 mg to

300 mg BID using a modified FOLFIRI regimen omitting the bolus (irinotecan 150 mg/m^2, 5-FU 2400 mg/m^2, leucovorin 400 mg/m^2). It is relevant to note that a CTEP-sponsored Phase 1 dose escalation study of veliparib in combination with FOLFOX independently reached the same conclusion that a 5-FU bolus is not tolerated with veliparib.[17] After 67 patients, the FOLFIRI dose was modified to irinotecan 180 mg/m^2, 5-FU 2400 mg/m^2 and a second dose escalation of veliparib starting at 100 mg BID was conducted. Leucovorin was removed from this regimen as there was a US supply shortage and it was deemed unnecessary due to the absence of a 5-FU bolus. Veliparib 200 mg BID was tolerated in this higher irinotecan dose. As doses exceeding veliparib 200 mg BID were not tolerated in the lower dose FOLFIRI regimen, further dose escalation was not pursued. The most common treatment-emergent adverse events, reported in ≥ 30% of all subjects, were diarrhea (57 subjects, 62.0%), nausea (55 subjects, 59.8%), vomiting (44 subjects, 47.8%), fatigue (43 subjects, 46.7%), alopecia (37 subjects, 40.2%), neutropenia (55 subjects, 60.9%), decreased appetite (30 subjects, 32.6%), and anemia (39 subjects, 42.4%). The most commonly reported treatment-emergent Grade 3 or 4 adverse events (rate > 5%) were neutropenia (33 subjects, 35.9%), anemia (9 subjects, 9.8%), diarrhea (5 subjects, 5.4%), dehydration (5 subjects, 5.4%) and hypokalemia (5 subjects, 5.4%). Two patients in the veliparib 270 mg BID dose level experienced dose-limiting toxicities (one patient with Grade 3 severe gastritis and Grade 3 vomiting and another patient with Grade 4 neutropenia). The recommended Phase 2 dose combination was determined to be veliparib 200 mg BID, irinotecan 180 mg/m^2, 5-FU 2400 mg/m^2, and leucovorin 400 mg/m^2. Although encouraging efficacy was noted in this study (17/96 PR, 42/96 SD), this was a heavily pre-treated population and thus efficacy comparisons with first-line FOLFIRI studies are not valid.

Additional details regarding clinical data can be found in the veliparib Investigator's Brochure.[14]

3.9 Benefits and Risks

This study proposes to establish improved clinical outcomes for patients with metastatic colorectal cancer (mCRC) through the addition of veliparib to FOLFIRI chemotherapy. Preclinical data demonstrate that veliparib potentiates the anti-tumor activity of topoisomerase inhibitors (such as irinotecan), and data from early-phase studies (completed or preliminary) is consistent with these observations. As described above, study subjects receiving veliparib with FOLFIRI have shown favorable, though not statistically significant, results for the endpoints of clinical benefit rate (response + stable disease) and progression-free survival. The current study is the first study to test colorectal cancer subjects receiving veliparib for improved progression-free survival that has sufficient power to detect a clinically meaningful benefit.

Risks in this study include toxicity from the addition of veliparib to standard therapy. Preliminary safety data from a Phase 1 study of the proposed combination suggest low rates of additional toxicities, and do not compromise the delivery of FOLFIRI, provided the 5-FU bolus is not used. Omission of the 5-FU bolus from FOLFIRI for subjects receiving veliparib deviates from standard of care, and may reduce the efficacy of chemotherapy. Veliparib may increase the likelihood subjects experience adverse events associated with FOLFIRI treatment. Standard clinical practices to manage the toxicity of FOLFIRI are well established. Other potential risks of veliparib administration, identified in preclinical studies or based on pharmacological mechanism, but not confirmed in clinical studies must also be considered. These risks include seizures, changes in testes/ovaries, toxicity to the developing fetus and secondary malignancies.

3.10 Differences Statement

There are differences in the study population and the underlying base chemotherapy regimen between this study and other ongoing studies. This study is the first randomized, blinded, multicenter, Phase 2 study comparing veliparib in combination with FOLFIRI ± bevacizumab to placebo in combination with FOLFIRI ± bevacizumab in subjects with previously untreated metastatic colorectal cancer. Other Phase 2 veliparib studies include:

Study M10-440: A randomized, Phase 2, double-blind, placebo-controlled study evaluating the efficacy of veliparib in combination with temozolomide versus temozolomide alone in subjects with metastatic melanoma.

Study M10-757: A randomized, Phase 2, open-label study in subjects with ovarian cancer receiving veliparib in combination with temozolomide versus pegylated liposomal doxorubicin alone.

Study M10-897: A randomized, Phase 2, double-blinded, placebo-controlled study in subjects with brain metastases from non-small cell lung cancer receiving veliparib and whole brain radiation therapy.

Study M10-898: A randomized, Phase 2, double-blinded, placebo-controlled study in subjects with untreated metastatic or advanced non-small cell lung cancer receiving veliparib plus carboplatin and paclitaxel.

Study M12-895: A randomized, Phase 2, double-blinded, placebo-controlled study in subjects with BRCA1 or BRCA2 mutation and metastatic breast cancer receiving veliparib plus carboplatin and paclitaxel.

4.0 Study Objective

The primary objectives of the study are to assess whether the addition of oral veliparib to FOLFIRI will improve progression-free survival (PFS) in subjects with previously untreated mCRC. The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), safety, and tolerability. The tertiary objectives are to assess duration of response (DOR) and the effects on a patient's Eastern Cooperative Oncology Group (ECOG) performance status (PS).

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a randomized, blinded, Phase 2 multicenter study evaluating the efficacy and tolerability of veliparib plus FOLFIRI versus placebo plus FOLFIRI in subjects with previously untreated metastatic colorectal cancer. At the discretion of the Investigator, subjects can also be treated with bevacizumab.

The study was designed to enroll approximately 120 subjects at approximately 60 study sites to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Subjects will be randomized to one of two protocol therapy groups as follows:

a. Veliparib plus FOLFIRI ± bevacizumab
b. Placebo plus FOLFIRI ± bevacizumab

Subjects will be stratified by the planned use of bevacizumab (planned bevacizumab use versus no planned use with bevacizumab) and regions of the world (North America versus rest of world). Randomization will be conducted to ensure that at least 60 subjects are enrolled in both the "planned bevacizumab use" group and "no planned bevacizumab use" group for a total of ~120 subjects. Subject randomization is detailed in Section 8.3.

Note that for the purposes of this protocol, FOLFIRI is used to describe both the standard regimen containing a 5-FU bolus that will be administered to subjects randomized to the placebo arm, and a modified regimen with a saline bolus that will be administered to subjects randomized to the veliparib arm. One cycle of protocol therapy consists of 14 days, defined as Day –2 through Day 12. Dosing of oral veliparib/placebo will begin 2 days prior to the start of FOLFIRI and will continue twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) may be

administered intravenously immediately preceding FOLFIRI. Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle. FOLFIRI is only to be given after veliparib/placebo dosing on cycle Day –2 and Day –1 are confirmed. An overview of the protocol schedule constituting one treatment cycle is shown in Figure 1. Additional details regarding dosing with veliparib/placebo, FOLFIRI and bevacizumab can be found in Section 5.5.

Guidelines for toxicity management and dose reductions or delays can be found in Appendix E, Appendix F, Appendix G, Appendix H, and Appendix I.

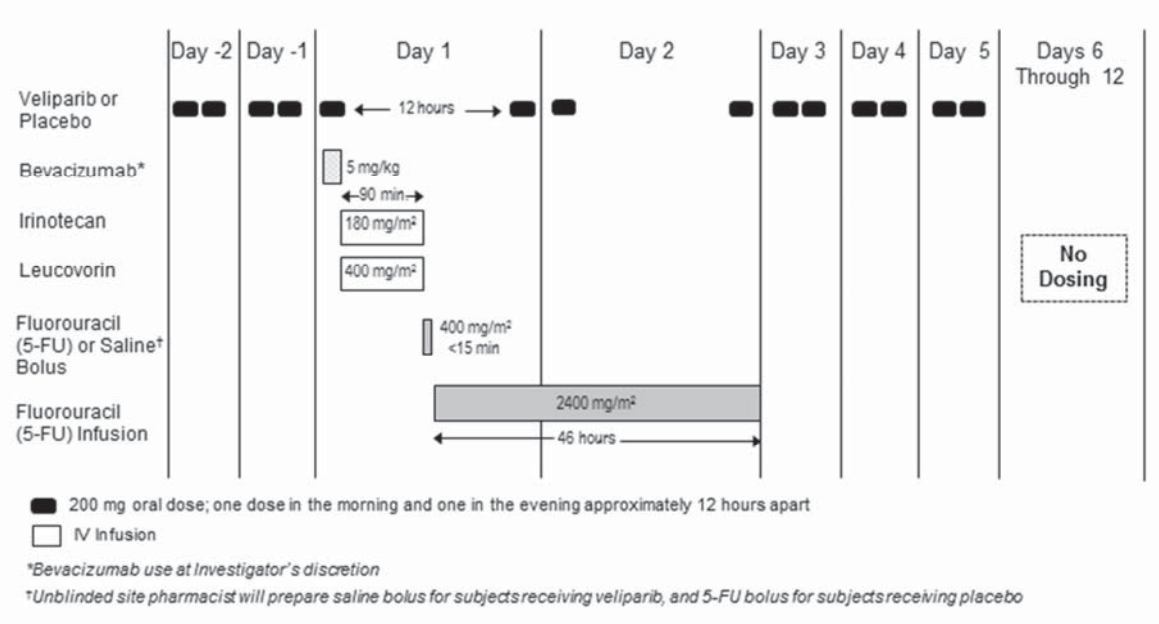
Screening procedures and baseline radiographic tumor assessments will be performed within 28 days prior to the first dose of veliparib/placebo on Cycle 1 Day –2 (C1D–2). Study visits will be conducted on Day 1 and Day 8 of the first and second cycle, then on Day 1 of each subsequent cycle. Subjects will continue protocol therapy and attending study visits until they meet one of the defined discontinuation criteria found in Section 5.4. When the Investigator has determined that a subject meets the criteria for discontinuation, a Final Visit will be conducted. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of protocol therapy.

Sites will begin collecting post-treatment and survival information 4 weeks after the last clinical assessment. Post-treatment and survival information is detailed in Section 5.4.5.

Details regarding study visits and study procedures can be found in Section 5.3 and Section 5.4.

Post-baseline radiographic tumor assessment will be conducted every 8 weeks from C1D1 (prior to the start of a new cycle) until radiographic progression. Radiographic tumor assessments will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.[18]

Figure 1. Protocol Therapy Dosing Schedule Overview



5.2 Selection of Study Population

The study population will consist of adult subjects with histologically or cytologically documented adenocarcinoma of the colon or rectum with metastatic disease, who have not received prior chemotherapy for their metastatic colorectal cancer.

5.2.1 Inclusion Criteria

1. ≥ 18 years of age;
2. Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum;

3. At least 1 unresectable lesion on a CT scan that is measurable as defined by RECIST, Version 1.1;
4. ECOG performance score of 0 or 1;
5. Adequate hematologic, renal and hepatic function as follows:
   - Bone marrow: Absolute Neutrophil Count (ANC) ≥ 1500/μL; Platelets ≥ 100,000/mm^3; (independent of platelet transfusions within 3 months prior to starting protocol therapy); Hemoglobin ≥ 9.0 g/dL;
   - Renal function: serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 50 mL/min;
   - Hepatic function and enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × the upper limit of normal (ULN) of institution's normal range. Subjects with liver metastases may have an AST and ALT of ≤ 5.0 × ULN;
   - Bilirubin: ≤ 1.5 × ULN of institution's normal range.
6. If female, subject must be postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing at least one of the following methods of birth control until 90 days after the last dose of protocol therapy:
   - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable;
   - Vasectomized partner(s);
   - Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior C1D–2 (if the subject is currently using a hormonal contraceptive, she should also use a barrier method during the study and for 1 month after protocol therapy completion);
   - Intrauterine device (IUD);
   - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams).

7. If male, subject must be surgically sterile or practicing at least one of the following methods of contraception, from the initial protocol therapy administration until 90 days after the last dose of protocol therapy:
   - Partner(s) using IUD;
   - Partner(s) using hormonal contraceptives (oral, vaginal, parenteral or transdermal);
   - Subject and/or partner(s) using double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams);
   - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable.
8. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Criteria Only For Subjects Receiving Bevacizumab

9. Blood pressure must be well controlled (< 160/90 mm Hg) on a stable regimen of anti-hypertensive therapy for at least two weeks.

Rationale for Inclusion Criteria

1 – 4	To select the appropriate subject population with sufficient disease severity for evaluation
5	For the safety of the subjects
6 – 7	The impact of veliparib on the unborn fetus is unknown; therefore, these criteria ensure that adequate precautions are taken to avoid pregnancy
8	In accordance with harmonized Good Clinical Practice (GCP)
9	For the safety of subjects that receive bevacizumab

5.2.2 Exclusion Criteria

1. Prior anti-cancer treatment for metastatic colorectal cancer;
2. Prior exposure to PARP inhibitors;
3. The last course of adjuvant or neoadjuvant chemotherapy must have ended > 12 months prior to C1D–2;
4. Known Gilbert's Syndrome;
5. Prior radiotherapy to greater than 25% of bone marrow;
6. Prior radiotherapy ≤ 4 weeks of C1D–2;
7. Any type of major surgery ≤ 4 weeks of C1D–2;
8. Previous or concurrent malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the subject has been disease-free for 3 years;
9. Known hypersensitivity to irinotecan, 5-FU or leucovorin;
10. Clinically significant and uncontrolled major medical condition(s) including but not limited to:
    - Uncontrolled nausea/vomiting/diarrhea;
    - Active uncontrolled infection;
    - Symptomatic congestive heart failure (NYHA Class ≥ II);
    - Unstable angina pectoris or cardiac arrhythmia;
    - Psychiatric illness/social situation that would limit compliance with study requirements.
11. Predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline pattern of > 3 watery of soft stools daily. Subjects with an ileostomy or colostomy may enter the study at the discretion of the Investigator;
12. Subject is pregnant or lactating;

13. Subject who requires parenteral nutrition, tube feeding or has evidence of partial bowel obstruction or perforation within 28 days prior to C1D–2;
14. Any medical condition, which in the opinion of the study Investigator, places the subject at an unacceptably high risk for toxicities;
15. Subject has received an investigational drug within the 28 days prior to Screening;
16. Any subjects will be excluded if prohibited from participation according to local laws or regulations.

Criteria Only For Subjects Receiving Bevacizumab:

17. Prior treatment with bevacizumab;
18. Known central nervous system metastases;
19. Significant history of bleeding events or GI perforation;
    - Subjects with a history of significant bleeding episodes (e.g., hemoptysis, upper or lower GI bleeding) within 6 months of C1D–2 are not eligible unless the source of bleeding has been resected;
    - Subjects with a history of GI perforation within 12 months of C1D–2 are not eligible.
20. Serious or non-healing wound, ulcer or bone fracture;
21. History of venous or arterial thromboembolism within 2 months of enrollment;
22. Known hypersensitivity to recombinant or murine antibodies.

Rationale for Exclusion Criteria

1 – 4, 7, 8, 11, 13, 16	To select the appropriate subject population with sufficient disease severity for evaluation
5, 6, 9, 10, 12, 14, 15	For the safety of the subjects
17 – 22	For the safety of subjects that receive bevacizumab

5.2.3 Prior and Concomitant Therapy

Any medication, therapy, or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving beginning with the Screening Visit, receives during the study, and up to 30 days following the last dose of protocol therapy must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. **Note:** Post-treatment cancer therapy information will be collected during survival (Section 5.4.5).

For purposes of this protocol, anti-cancer treatment, medication or therapy is defined as, but not limited to: anti-cancer agents (cytotoxic chemotherapy, immunotherapy, biologic therapy and/or radiation therapy) and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

For the purposes of study eligibility, subjects who have not received prior systemic chemotherapy after the diagnosis of metastatic colorectal cancer are considered "previously untreated."

General guidelines regarding cautionary, excluded, and permitted concomitant medications/therapies are summarized in Table 1, Table 2, and Table 3.

The locally approved product label or applicable Summary of Product Characteristics (SmPC) for irinotecan, leucovorin, and 5-FU should also be referenced for any concomitant therapy guidelines.

Additional guidance for the use of concomitant medications is provided in the Toxicity Management Guidelines for Protocol Therapy (Appendix E, Appendix F, Appendix G, Appendix H, and Appendix I).

The AbbVie Study Designated Physician identified in Section 6.7 should be contacted if there are any questions regarding prior therapy(ies) or concomitant medications/therapies.

Table 1. Cautionary Medications

Medication/Therapy	Comments
Therapies to Take Caution with When Administered with Irinotecan:	**Strong CYP3A4 Inducers:** Anticonvulsants and other strong inducers: Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in subjects concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants such as phenytoin, phenobarbital or carbamazepine. **Consideration should be given to substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy.** St. John's Wort: Exposure to the active metabolite SN-38 is reduced in patients receiving concomitant St. John's Wort. **St. John's Wort should be discontinued at least 2 weeks prior to the first cycle of protocol therapy.**
	Strong CYP3A4 Inhibitors: Discontinue at least 1-week prior to starting irinotecan therapy and do not use during irinotecan therapy. **Ketoconazole is a strong inhibitor of CYP3A4 enzymes.** Subjects receiving concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38. Subjects should **discontinue ketoconazole at least 1-week prior to starting** protocol therapy.

Table 2. Excluded Medications

Medication/Therapy	Comments
Anti-Cancer Treatment	**Not permitted** prior to enrollment and during protocol therapy; this includes hormonal therapy administered with the intent of using it as an anti-cancer therapy.
PARP Inhibitors	**Not permitted** prior to enrollment and during protocol therapy.
Alternate Therapy	Herbal remedies or non-prescription supplements with the intent of using them as an anti-cancer therapy **are not permitted ≤ 2 weeks prior to C1D–2 and during protocol therapy.**
Ketoconazole	**Not permitted** during irinotecan therapy.
St. John's Wort	**Not permitted** during irinotecan therapy.

Table 3. Concomitant Medications/Therapies

Medication/Therapy	Comments
Premedication for Leucovorin	Refer to the locally approved product label or applicable SmPC
Premedication for Fluorouracil	Refer to the locally approved product label or applicable SmPC
Premedication for Irinotecan	Refer to the locally approved product label or applicable SmPC
Premedication for Bevacizumab	Refer to the locally approved product label or applicable SmPC
Supportive Care:	**Permitted:** Best supportive care and treatment can be given as appropriate to each subject, including but not limited to anti-emetics, anti-diarrheal, antibiotics, steroids for adrenal failure, hormonal therapy administered for non-disease related conditions, blood and blood products, nutritional support, palliative treatment for pain, etc.
Growth Factors:	**Permitted:** Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) may be administered during protocol therapy. Granulocyte growth factors (e.g., G-CSF, GM-CSF, etc.) are to be administered according to the Investigator's standard practice and/or NCCN guidelines, 2014. Growth factors may be given with the intent to prevent dose reductions or delays.
Non-disease Related Surgery:	Non-disease related surgery during protocol therapy is permitted; however, the AbbVie Study Designated Physician must be contacted. For patients receiving bevacizumab, refer to locally approved product information for specific guidelines regarding surgery.
Disease Related Surgery:	Disease related surgery during protocol therapy is permitted; however, the AbbVie Study Designated Physician must be contacted. For subjects receiving bevacizumab, refer to locally approved product information for specific guidelines regarding surgery.

5.3 Efficacy Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of study activities are outlined in Table 4. The schedule of pharmacokinetic, pharmacodynamics and pharmacogenetic assessments are presented in

Table 5 and Table 6. The procedures outlined in Table 5 and Table 6 are discussed in detail in Section 5.3.2.

Table 4. Study Assessments

Activity*^	Screening	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Day 1 of Each Cycle	Every 8 Weeks from C1D1^	Final Visit[a]	30-Day Follow-Up Visit[b]	Survival Period[c]
Informed Consent[d]	X										
Medical and Cancer History	X										
Physical Exam	X[e]	X[e]			X		X		X	X	
Subject Weight	X		X		X		X				
12-lead ECG	X								X		
Vital Signs	X	X	X		X		X		X	X	
Performance Status (ECOG)	X		X		X		X		X		
Pregnancy Test[f]	X	X									
Hematology[g]	X	X	X	X	X	X	X		X	X	
Chemistry[g]	X	X	X	X	X	X	X		X	X	
Urinalysis[g]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]				
aPTT/PT/INR[g]	X										
CEA	X							X[i]			
Tumor Assessments	X[j]							X[j]	X		
Randomization[k]		X									

Table 4. Study Assessments (Continued)

Activity*^	Screening	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Day 1 of Each Cycle	Every 8 Weeks from C1D1^	Final Visit[a]	30-Day Follow-Up Visit[b]	Survival Period[c]
Dispense veliparib/placebo[l]		X	X		X		X				
Administer Veliparib/Placebo at the site[m]		X	X		X		X				
Administer Bevacizumab[k]			X		X		X				
Administer FOLFIRI[n]			X		X		X				
AE Assessments[o]	X	X	X	X	X	X	X		X	X	
Prior and Concomitant Therapy Assessments	X	X	X	X	X	X	X		X	X	
Post-treatment Cancer Information											X
Date and Cause of Death											X

* Refer to Table 5 and Table 6 for the schedule of PK, PG, and PD assessments.

^ Subjects who discontinue protocol therapy prior to reaching an event of disease progression are to continue attending study visits and radiographic assessments until progression.

For all study procedures: At the discretion of the Investigator, additional monitoring can be done if clinically indicated.

Timing of Study Procedures: Screening procedures must be performed within 28 days prior to C1D–2. For procedures performed at Screening then repeated on C1D–2 prior to dosing, the later procedure(s) will serve as baseline for clinical assessment and must still meet all eligibility criteria. Subsequent study visits may be performed 4 days surrounding (± 2 days) the scheduled visit date, with the exception of scheduled tumor assessments and laboratory tests. Tumor assessments can be performed up to 4 days prior to a scheduled tumor assessment, but should be performed prior to administration of the next scheduled cycle of FOLFIRI. Clinical laboratory tests must be performed up to 48 hours prior to dosing, not after dosing.

Table 4. Study Assessments (Continued)

a. When an Investigator has determined that a subject should discontinue protocol therapy and attending study visits, a Final Visit will be conducted.
b. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of protocol therapy. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.
c. Sites will be collecting survival information and post-treatment cancer information beginning 4 weeks after the last study visit and continuing every 4 weeks for 1 year, then every 8 weeks for up to 2 additional years or until the endpoint of death.
d. Must be performed prior to initiation of any screening or study specific procedures.
e. Height is only measured at Screening. Physical exam is not required on C1D–2 if one has been performed within the last 7 days.
f. For women with potential childbearing status, serum pregnancy test will be done at Screening. Urine pregnancy test will be done prior to dosing at C1D–2 unless the serum pregnancy test was collected within 7 days of C1D–2. Subjects with non-childbearing status do not require pregnancy tests.
g. All laboratory samples will be assessed using a central laboratory and these data will be used for all data analysis. A local reference laboratory may perform chemistry, hematology, coagulation, and urinalysis tests for immediate subject management (i.e., emergent situations); however, split or concurrent samples must be drawn and sent to the central laboratory for analysis.
h. Urinalysis is required for all subjects at Screening. Subsequent testing is then only required for those that are receiving bevacizumab. For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection or urine protein to creatinine (UPC) ratio. Refer to Appendix I (Proteinuria) for additional guidance.
i. A CEA blood test will only need to be repeated if it is elevated above ULN at baseline.
j. Baseline tumor assessments must be conducted within 28 days prior to C1D–2. Post-baseline tumor assessment will be conducted every 8 weeks from C1D1 until radiographic progression. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Tumor assessments should be conducted prior to the start of the next scheduled cycle of FOLFIRI. An unscheduled tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression, and no scan has been performed within the last 4 weeks.
k. Bevacizumab use is optional. Investigators must declare their planned use of bevacizumab at the time of randomization.
l. Sufficient medication will be dispensed to cover the remaining cycle and pre-dosing for the subsequent cycle.
m. On days that pre-dose PK and PD sampling is required (refer to Table 5 and Table 6), dosing will occur in the morning at the site to facilitate PK and PD sampling. Instruct subjects not to take veliparib/placebo at home.
n. FOLFIRI is to be given only after veliparib/placebo dosing on Day –2 and Day –1 of each cycle is confirmed. Site pharmacy personnel will be unblinded and should prepare the bolus **with** 5-FU for subjects randomized to the placebo arm and **without** 5-FU for subjects randomized to the veliparib arm.
o. See Section 6.6, Adverse Event Collection, for details.

Table 5. Schedule of Pharmacokinetic (PK) Assessments

Procedure	Visit Schedule	Before Drug Administration	After Veliparib AM Dose	Sampling Plan Specimen Matrix
Veliparib PK Sampling	C1D–2	--	1, 2, 3 h	Blood → Plasma Frozen (as per the study specific laboratory manual)
Veliparib PK Sampling[a]	C2D1 and C3D1	0 h[a]	--	Blood → Plasma Frozen (as per the study specific laboratory manual)

a. Before the administration of the morning dose of veliparib/placebo. Veliparib/placebo dosing will occur in the morning at the site to facilitate PK sampling. Instruct subjects not to take the morning dose of veliparib/placebo at home.

Table 6. Schedule of Pharmacogenetic (PG) and Pharmacodynamic (PD) Assessments

Activity	Visit Schedule	Before Drug Administration	Sampling Plan Specimen Matrix
Optional with Consent PG Blood Sampling* Genetic (DNA)	C1D–2 Final Visit	Not applicable	Whole Blood Frozen (as per the study specific laboratory manual)
PD Blood Sampling Plasma Markers[a,b]	C1D–2, C2D1, Final Visit	Pre-dose** At the time of the study visit	Blood → Plasma Frozen (as per the study specific laboratory manual)
Serum Markers[c]	C1D–2, C2D1, Final Visit	Pre-dose** At the time of the study visit	Blood → Serum Frozen (as per the study specific laboratory manual)
Tissue Sample Collection	Screening[d]		Archived FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)
MSI Testing Control Sample	C1D–2	N/A	Blood Frozen –20°C or colder

* (Optional) only to be collected after additional informed consent is obtained.

** Veliparib/placebo dosing will occur in the morning at the site to facilitate PD sampling. Instruct subjects not to take the morning dose of veliparib/placebo at home.

a. At C1D–2 and the Final Visit, 12 mL of blood for plasma markers will be collected. At C2D1, it will be 6 mL of blood.

b. Processing should be completed in less than 60 minutes of sample being drawn.

c. Processing should be completed in less than 90 minutes of sample being drawn.

d. Sites should make every effort to obtain archived, diagnostic tissue sample by the C3D1 study visit.

5.3.1.1 Study Procedures

The study procedures outlined in Table 4 are discussed in detail in this section, with the exception of administering protocol therapy (Section 5.5), Final Visit (Section 5.4.3), 30-day Safety Follow-Up Visit (Section 5.4.4), and Survival and Post-Treatment Cancer Information (Section 5.4.5). All study data will be recorded on electronic case report forms (eCRFs).

For all study procedures: The study procedures outlined in this protocol are recommendations based on routine safety assessments required during chemotherapy and veliparib administration. At the discretion of the Investigator, additional monitoring can be done whenever clinically indicated.

Timing of Study Procedures

Screening procedures must be performed within 28 days prior to C1D–2. For procedures performed at Screening then repeated on C1D–2 prior to dosing, the later procedure(s) will serve as baseline for clinical assessment and must still meet all eligibility criteria. Subsequent study visits may be performed 4 days surrounding (± 2 days) the scheduled visit date, with the exception of the following:

- If the Screening physical examination is performed within 7 days of C1D–2, it is not required to repeat the exam on C1D–2 unless clinically indicated.
- Tumor assessments can be performed up to 4 days prior to a scheduled tumor assessment, but should be performed prior to administration of the next scheduled cycle of FOLFIRI.
- Clinical laboratory tests should be performed up to 48 hours prior to dosing.

Informed Consent

Signed informed consent will be obtained from the subject before any study procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study.

A separate optional informed consent will be required for pharmacogenetic testing. Details about how informed consent will be obtained and documented are provided in Section 9.3.

In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained. Details about how informed consent will be obtained and documented are provided in Section 6.8.

Subjects will be considered screen failures if the informed consent has been signed and a study specific procedure has been performed (e.g., central labs drawn), but subject does not randomize into the study. The informed consent process for subjects will be repeated in the event the site obtains written permission from the AbbVie Study Designated Physician to re-screen a subject for the study.

Medical History

A complete medical history, including documentation of the following:

- Clinically significant medical condition(s);
- History of tobacco and alcohol use;
- Surgical history;
- Date subject was diagnosed with colorectal cancer and pathology information;
- RAS status (if known);
- BRAF status (if known);
- Microsatellite instability (MSI) status (if known).

On C1D–2 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. At each subsequent visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF.

Physical Examination and Body Weight

A physical examination will be performed per Table 4. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Body weight will be measured only at the visits identified in Table 4.

Height will be measured at the Screening Visit only. For height and weight assessments, the subject should not wear shoes.

Vital Signs

Vital signs will be performed per Table 4. Vital sign determinations include sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Table 4. A qualified physician will determine whether any findings outside of normal physiological variation are clinically significant (in consultation with a cardiologist if necessary). The physician will document whether findings are clinically significant or not clinically significant on the tracing and sign and date the tracing. The original annotated ECG tracing along with a photocopy of the tracing containing the physician's assessment will be retained in the subject's records at the study site.

ECOG Performance Status

The ECOG performance status will be assessed per Table 4 as follows:

Grade	ECOG
0	Fully Active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Documentation of Non-Childbearing Status or Pregnancy Test

For each female subject, the Investigator will document non-childbearing status (surgically sterile or post-menopausal for at least 1 year) or potential childbearing status. Subjects with non-childbearing status do not require pregnancy tests. For subjects of childbearing potential, a serum pregnancy test will be performed at Screening and the results must be available prior to the administration of the first dose of protocol therapy on C1D–2. A urine pregnancy test should also be performed prior to dosing on C1D–2 if > 7 days since obtaining Screening serum test results. The test results must be reviewed and determined to be negative prior to dosing. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Pregnancy tests may also be repeated at the discretion of the Investigator at any time during the study.

Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the Investigator immediately (Section 6.8). Subjects with confirmed pregnancy must immediately discontinue protocol therapy and must be discontinued from the study.

Clinical Laboratory Tests

Laboratory samples will be collected per Table 4. Specific laboratory tests are listed in Table 7. Qualified medical staff at the site will review, initial and date all local and central laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.0.

All laboratory samples will be assessed using a central laboratory and these data will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing, handling, and shipping of samples. All clinical laboratory samples will be shipped to the central laboratory.

A local reference laboratory may perform chemistry, hematology, coagulation, and urinalysis tests for immediate subject management (i.e., emergent situations); however, split or concurrent samples *must* be drawn and sent to the central laboratory for analysis. The appropriate certifications will be collected for both the central and local laboratories as needed.

If there is a discrepancy between the local and central labs, the site must enter the relevant local labs that were used for treatment decisions on the appropriate eCRF.

Table 7. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate/CO^2 Estimated Glomerular Filtration Rate (eGFR)	Specific gravity Ketones pH Protein* Blood Glucose
		Tumor Marker
		Carcinoembryonic antigen (CEA)**
Coagulation Tests		**Serum Pregnancy Test**
Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ratio (INR)		*Human Chorionic Gonadotropin* (*hCG*)***

* For proteinuria of ≥ 2+, confirm total urine protein with a 24-hour urine collection.

** A CEA will only need to be repeated after screening if elevated above the ULN at baseline.

*** At Screening and at any time point in which pregnancy is suspected or following a positive urine pregnancy test.

Tumor Assessments (Radiologic)

A CT scan of all areas of metastatic disease (including the neck, chest, abdomen, and/or pelvis (where appropriate) using RECIST, Version 1.1 will be used in the evaluation of tumor responses. If the subject is unable to undergo a CT scan with IV contrast due to allergy or renal insufficiency, a non-contrast CT may be performed. Magnetic resonance imaging (MRI) can be conducted instead of CT scans in cases where local laws/requirements mandate or when an MRI would be a better tool for tumor assessments. Subjects are to continue monitoring by the same methods unless evidence of tumor metastasis warrants otherwise or a medical contraindication is noted.

Baseline tumor assessments must be conducted within 28 days prior to C1D–2. Post-baseline tumor assessment will be conducted every 8 weeks from C1D1 until radiographic progression. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Scheduled tumor assessments should be performed prior to the administration of the next cycle of FOLFIRI. An unscheduled tumor assessment should be performed if the subject discontinues from the study for a reason other than radiographic progression, and no scan has been performed within the last 4 weeks.

For the purposes of this protocol, complete or partial responses do not need to be confirmed on a subsequent scan following initial documentation of the response.

AbbVie may require that sites electronically transfer copies of all CT or MRI scans used for radiographic tumor assessments. Instructions regarding procedures for transferring scans will be provided in a separate manual.

Randomization and Subject Number Assignment

An IRT system will be utilized to register subjects on study. The site will contact the IRT to obtain a screening (subject) number once the subject has signed informed consent and a study specific procedure has been performed (e.g., central labs drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source and captured in the IRT system and documented in the eCRF.

Subjects who complete all screening procedures and meet the eligibility criteria can proceed to randomization. The site will access the IRT and a unique randomization number will be provided. During the randomization process, subjects will be randomized in a 1:1 ratio to either veliparib 200 mg BID plus FOLFIRI or placebo BID plus FOLFIRI (bevacizumab will be administered at the discretion of the Investigator).

Note: The use of bevacizumab must be known prior to randomization and when accessing the IRT for randomization.

A bottle number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IRT vendor.

5.3.2 Drug Concentration Measurements

5.3.2.1 Blood Samples for Pharmacokinetic Analysis

Veliparib Pharmacokinetic Specimen Collection

The date and time of each blood sample collection will be recorded. The date and time of the veliparib/placebo dose on PK sampling days (refer to Table 5) and the date and time of the two doses of veliparib/placebo prior to PK sampling on C2D1 and C3D1 will be captured on the eCRF. Blood samples (3 mL) will be collected by venipuncture into evacuated potassium (K_2) EDTA tubes per Table 5.

Sufficient blood will be collected to produce approximately 1 mL of plasma for each sample.

Processing and Shipment of Pharmacokinetic Samples

All samples should be processed, labeled and shipped as outlined in the study specific laboratory manual. An inventory of the samples being shipped will accompany the package.

5.3.2.2 Measurement Methods

Plasma concentrations of veliparib will be determined using a validated method under the supervision of the Drug Analysis Department at AbbVie. Additionally, veliparib metabolite(s) concentrations in plasma samples may be determined using a non-validated or a validated assay.

5.3.2.3 Blood Samples for Pharmacogenetic Analysis

Two 4 mL whole blood sample for DNA isolation will be collected from each subject who consents to provide a sample for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. The first sample will be collected at C1D–2 and the second sample will be collected at the final visit.

The sample collection tubes will minimally be labeled with "PG-DNA blood," protocol number, subject number and visit. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the lab manual.

AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on Veliparib (or drugs of this class) continues but no longer than 20 years.

5.3.2.4 Blood Samples for Pharmacodynamic Analysis

Pharmacodynamic correlative studies are exploratory in nature. Serum, plasma and tissue specimens may be utilized to evaluate known and novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status. PD variables will be further discussed in Section 5.3.7.

Blood Collection for Plasma Markers

Twelve (12) mL or 6 mL of blood will be collected pre-dose by venipuncture at timepoints outlined in Table 6 in conjunction with PK samples, if possible. The collection, processing and storage should be performed as described in the study specific laboratory manual. The complete process of centrifugation, transfer to cryovial and freezing should be accomplished in less than 1 hour from the time of blood draw.

Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected pre-dose by venipuncture at timepoints as outlined in Table 6. The collection, processing and storage should be performed as described in the study specific laboratory manual. The complete process of clot formation, centrifugation, transfer to cryovials and freezing should be accomplished in less than 90 minutes from the time of blood draw.

Archived Tissue Collection

Subjects must provide available archival tissue for analysis. The most recent archived biopsy is preferred and should be obtained during screening if possible; however, every effort should be made to obtain the tissue sample by the C3D1 study visit. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study specific laboratory manual. Study specific biopsies are not required for subject participation.

Collection of MSI Testing Control Sample

One 4 mL whole blood sample for DNA isolation will be collected at C1D–2 from each subject. The collection, processing and storage should be performed as described in the study specific laboratory manual.

Shipment of Pharmacodynamic Samples

All samples should be labeled and shipped as outlined in the study specific laboratory manual. An inventory of the samples being shipped will accompany the package.

5.3.3 Efficacy Variables

Disease progression will be defined as clinical progression as determined by the Investigator, or radiographic progression of disease by RECIST, Version 1.1 (Appendix D).[18]

5.3.3.1 Primary Variable

The primary efficacy endpoint is progression-free survival.

5.3.3.2 Secondary Variables

Secondary efficacy endpoints are overall survival (OS) and objective response rate (ORR).

5.3.3.3 Tertiary Variables

The tertiary efficacy endpoints are duration of overall response (DOR) and Eastern Cooperative Oncology Group (ECOG) performance status.

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, and vital signs. Adverse events will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE Version 4.0.[19] During the conduct of the study, the AbbVie medical and safety team will be monitoring subject laboratory results and serious adverse event data as it is reported.

The AbbVie Study Designated Physician and safety team will review individual patient safety data during planned interim analyses and aggregate safety data on a regular basis for continued safety assessment.

5.3.5 Pharmacokinetic Variables

A nonlinear mixed effect modeling analysis will be conducted to estimate the population pharmacokinetic parameters of veliparib such as apparent oral clearance (CL/F) and volume of distribution (V/F).

AbbVie or a designated laboratory will store the pharmacokinetic samples in a secure storage space with adequate measures to protect confidentiality. To increase confidence in trends, remaining sample aliquots may be used to perform replicate tests, or sample

analysis at additional time points for tests currently identified in the protocol. Upon completion of this research AbbVie or a designated laboratory will destroy the samples.

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to veliparib (or other study treatment) in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to veliparib, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to veliparib, drugs of this class, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.7 Pharmacodynamic Variables

Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of exploring the relationship between tumor response and/or disease status.

Biospecimens collected may be evaluated for genetic lesions whether they occur by amplification, chromosomal loss and/or mutational/methylation with the intent of identifying potential associations with subject outcome or to better characterize the disease. These characterizations may be included, but are not limited, characterization of gene methylation/mutational status or copy number changes of genes, particularly those involved in DNA repair pathways. Additional analysis aimed at identifying underlying defects in the homologous recombination pathway, regardless of etiology, may be performed and associated with response.

Biospecimens may be evaluated for levels of biomarkers including nucleic acids, proteins/peptides and metabolites. For example, protein analysis of relevant proteins,

including but not limited to, DNA repair proteins, such as ERCC1 and XPF, may be performed on tumor tissue obtained from each consented subject.

AbbVie (or people or companies working with AbbVie) will store and analyze the samples in a secure space with adequate measures to protect confidentiality. Samples will be retained up to 20 years (or per local legal requirement) while research on veliparib (or drugs of this class) or colorectal cancer (or related conditions) continues.

5.4 Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits

Each subject also has the right to withdraw from the study (withdraw from protocol therapy and attending scheduled study visits) at any time. In addition, the Investigator may discontinue a subject from the study at any time for any reason if the Investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol.

In the event a subject withdraws consent from participating in the study, stored pharmacodynamic samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research of samples, the subject may request for samples to be withdrawn. Once AbbVie receives the request, remaining samples will be destroyed unless the FDA requires AbbVie to keep the samples. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

When subject discontinuation from the study is planned without the subject reaching a protocol-defined endpoint, the Investigator will notify the individuals listed in Section 7.0 via telephone and/or email, as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to study discontinuation, the AbbVie Study Designated Physician or designee may contact the site to discuss the reason for withdrawal from the study.

The Investigator, or designee, must report when a subject discontinues protocol therapy and/or scheduled study visits in the IRT system. After a subject discontinues protocol therapy and stops attending scheduled study visits they will be followed for survival and post-treatment cancer information for up to 3 years or until the end point of death.

5.4.1 Discontinuing Subjects from Protocol Therapy

Tumor Response

Subjects who achieve a CR, PR, or SD should continue on protocol therapy until intolerable toxicity, or if there is documented clinical or radiographic progression.

Clinical data that supports colorectal progression will be collected on the appropriate eCRF.

Surgical Intervention

As a result of treatment, subjects may suspend protocol therapy to undergo surgical resection with curative intent for metastatic disease. Subjects may then restart protocol therapy beginning with the next scheduled cycle provided they have recovered from surgery and the Investigator believes that continuing treatment would be in the best interests of the subject. With respect to tumor measurements, subjects who undergo surgical resection must undergo radiographic assessment within 14 days of resuming protocol therapy. This scan will serve as the new post-surgery baseline. Target or non-target lesions existing before and remaining after surgery should continue to be evaluated using RECIST, Version 1.1. Subjects can remain on study until there is clinical or radiographic disease progression (i.e., a new lesion) or the subject meets other discontinuation criteria. Investigators should refer to locally approved product information guidelines before any surgical intervention. Details regarding tumor response measurements can be found in Appendix D.

Additional Criterion for Discontinuation of Protocol Therapy

Subjects will discontinue protocol therapy if any of the following occur:

- The subject experiences unacceptable protocol therapy toxicity (refer to Appendix E, Appendix F, Appendix G, Appendix H, and Appendix I) or the Investigator believes it is otherwise in the best interest of the subject;
- Subject is suspected to be pregnant; pregnancy is confirmed or begins breastfeeding during the treatment portion of the study;
- The subject decides to withdraw consent for any reason;
- Any other medical reason that AbbVie or the Investigator deems appropriate.

The Investigator, or designee, must report when a subject discontinues protocol therapy for any reason in the IRT.

5.4.2 Discontinuing Subjects from Study Visits

When subjects reach an event of disease progression, a Final Visit and 30-Day Safety Follow-Up Visit should be conducted.

Subjects who discontinue protocol therapy prior to reaching an event of disease progression should continue to receive radiographic assessments per Table 4 until documented clinical or radiographic disease progression is experienced, if possible.

The Investigator, or designee, must report when a subject stops attending scheduled study visits in the IRT.

5.4.3 Final Visit

When a subject discontinues protocol therapy, a Final Visit will be conducted (preferably prior to the initiation of another anti-cancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the protocol therapy, the subject will be treated in accordance with the Investigator's best clinical judgment.

At the Final Visit, the reason(s) for the discontinuation from the study will be recorded and assessments will be performed per Table 4.

5.4.4 Follow-Up Visit

All subjects will have one Follow-Up Visit approximately 30 days after the last dose of protocol therapy. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

5.4.5 Timing and Collection of Survival and Post-Treatment Cancer Information

Subjects who discontinue protocol therapy will be followed for survival (the date and cause of death or last known alive date if not deceased) and post-treatment cancer information. Sites will collect survival information and post-treatment cancer information beginning 4 weeks after the last clinical assessment and continuing every 4 weeks for 1 year, then every 8 weeks for up to 2 additional years or until the endpoint of death. Survival and post-treatment cancer information will be collected in the electronic data capture (EDC) system.

Every effort should be made by study staff to follow each subject for survival and post-treatment cancer information. In the event a subject no longer wants to be contacted, they must specifically withdraw consent from the collection of survival and post-treatment cancer information collection. Study staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

5.4.6 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination.

Advance notice is not required by either party if the study is stopped due to safety concerns.

The following procedures for study discontinuation will be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify in writing each Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- Each Investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation.
- Each Investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Protocol Therapy Administered

Subjects will be randomized to one of the following protocol therapy groups:

- Veliparib 200 mg PO BID Day –2 through Day 5 plus modified FOLFIRI (irinotecan IV 180 mg/m^2; leucovorin IV 400 mg/m^2; saline IV bolus; 5-FU IV 2400 mg/m^2) ± bevacizumab (5 mg/kg) administered on Day 1 of each 14-day cycle;
- Placebo 200 mg PO BID Day –2 through Day 5 plus standard FOLFIRI (irinotecan IV 180 mg/m^2; leucovorin IV 400 mg/m^2; 5-FU IV 400 mg/m^2 bolus; 5-FU IV 2400 mg/m^2) ± bevacizumab (5 mg/kg) administered on Day 1 of each 14-day cycle.

Dispensing Protocol Therapy

Randomized subjects will receive sufficient quantities of veliparib/placebo for Cycle 1 Days –2 to 1 by dispensing on C1D–2. Beginning with C1D1, subjects will receive veliparib/placebo for Days 1 – 5 of the current cycle and a separate bottle for Days –2 and

–1 of the following cycle. This dispensing schedule will allow subjects to begin veliparib/placebo dosing prior to the start of the next FOLFIRI cycle without requiring a return to the investigative site prior to FOLFIRI administration. The IRT will assign every bottle of study drug to be dispensed to a subject. Prior to each scheduled drug dispensation visit, site personnel must contact IRT for the next bottle number assignment. Study medication cannot be dispensed without contacting the IRT. AbbVie or designee will provide specific instructions on the use of IRT.

FOLFIRI and bevacizumab should be obtained commercially via the site pharmacy. Site pharmacy personnel should prepare the bolus **with** 5-FU for subjects randomized to the placebo arm, or **without** 5-FU for subjects randomized to the veliparib arm. Site pharmacy personnel are responsible for ensuring that the appearance of the bolus does not compromise the blind for the subject, Investigator, or other site staff. Trained site personnel will administer FOLFIRI and bevacizumab (if the Investigator chooses to use bevacizumab) intravenously on Day 1 of each 14-day cycle. Subjects will be supervised at the time of the infusion.

FOLFIRI and bevacizumab are to be given only after veliparib/placebo dosing on cycle Day –2 and Day –1 are confirmed. If veliparib/placebo was not taken by the subject on Day –2 and Day –1, a new supply of veliparib is to be dispensed, and Day –2 and Day –1 are to be repeated for that cycle.

Sites may calculate body surface area (BSA) per local treatment practice. Bevacizumab and FOLFIRI doses should be calculated based on the weight measurement obtained at C1D1. Subsequent bevacizumab and FOLFIRI doses must be recalculated if a subject's body weight increases or decreases by more than 10%.

On days that pre-dose PK and PD sampling is required (refer to Table 5 and Table 6), dosing of veliparib will occur in the morning at the clinic to facilitate PK and PD sampling.

Administration of Veliparib/Placebo

Subjects will self-administer the morning dose of veliparib/placebo and the evening dose of veliparib/placebo approximately 12 hours after the morning dose with or without food in the same calendar day.

It is recommended that if a subject misses a scheduled dose of veliparib/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait for the next regularly scheduled dose.

If the subject vomits within 15 minutes of taking veliparib/placebo, another dose is to be taken. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken. The subject is to contact the Investigator if additional veliparib/placebo is needed to complete BID dosing through Day 5 of the cycle.

Subjects will be provided self-administration instructions and subject dosing cards to record the date and time the veliparib/placebo was administered. Subjects will be instructed to store veliparib/placebo according to specific directions included in Section 5.5.6. Subjects should return bottles of veliparib/placebo (empty, partially filled or full) to the study site prior to each cycle and at the Final Visit.

Administration of Irinotecan

For the purposes of this protocol, irinotecan 180 mg/m^2 will be administered as a 90 minute (± 30 minutes) IV infusion on Day 1 of each 14-day cycle. Investigators should evaluate subjects for irinotecan treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Leucovorin

For the purposes of this protocol, leucovorin 400 mg/m^2 will be administered as a 90 minute (± 30 minutes) IV infusion concurrent with irinotecan on Day 1 of each 14-day cycle. Irinotecan and leucovorin may be administered sequentially in accordance with local practice. Investigators should evaluate subjects for leucovorin treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Fluorouracil (5-FU) Bolus

For the purposes of this protocol, administration of a 5-FU bolus will be contingent on whether subjects are randomized to the veliparib or placebo arm. For subjects randomized to the placebo arm, a 5-FU 400 mg/m^2 bolus (up to 15 minutes) will be administered. For subjects randomized to the veliparib arm, a saline bolus (up to 15 minutes) will be administered. Site pharmacy personnel will have access to the treatment arm assignment via the IRT system and should prepare the bolus accordingly. Investigators should evaluate subjects for 5-FU treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Fluorouracil (5-FU) Infusion

For the purposes of this protocol, 5-FU 2400 mg/m^2 will be administered as a 46-hour (± 4 hours) IV infusion on Day 1 of each 14-day cycle. Investigators should evaluate subjects for 5-FU treatment per the locally approved product label, local practice, or applicable SmPC.

Administration of Bevacizumab

At the discretion of the Investigator, bevacizumab may be administered at 5 mg/kg intravenously immediately preceding FOLFIRI on Day 1 of each 14-day cycle. The initial dose of bevacizumab should be given over 90 minutes (± 30 minutes), second dose over 60 minutes (± 20 minutes), and all subsequent doses over 30 minutes (± 10 minutes) if prior infusions are tolerated without infusion associated adverse events.

Order of Administration

Protocol therapy will be administered in the following order: veliparib/placebo **followed by** FOLFIRI as irinotecan **concurrent with** leucovorin **followed by** a saline or 5-FU bolus **followed by** 5-FU infusion. For the purposes of this protocol, veliparib/placebo should always be given first.

Irinotecan and leucovorin may be administered sequentially in accordance with local treatment practice.

At the Investigator's discretion, bevacizumab may be administered at 5 mg/kg intravenously after veliparib/placebo and immediately preceding FOLFIRI on Day 1 of a 14-day cycle.

Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese subjects when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the subject's actual weight without any modification. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Investigators who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese subjects.

5.5.2 Toxicity Management and Protocol Therapy Dose Reductions or Delays

Specific guidelines for toxicity management and dose reductions or delays for protocol therapy are discussed in Appendix E (General Guidelines), Appendix F (Dose Reductions for Veliparib/Placebo), Appendix G (Dose Reductions for FOLFIRI), Appendix H (Dose Reductions for Bevacizumab) and Appendix I (Toxicity Management).

5.5.3 Identity of Investigational Product

Information regarding the veliparib and placebo formulation to be used in this study is presented in Table 8.

Table 8. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Veliparib (ABT 888)	Capsule	50 mg	Oral	AbbVie
Placebo	Capsule	50 mg placebo	Oral	AbbVie

AbbVie will supply veliparib capsules and a matching placebo for veliparib.

5.5.4 Standard of Care Medicinal Products

Information regarding FOLFIRI and bevacizumab to be used in this study is presented in Table 9.

Table 9. Standard of Care Medicinal Products

Study Drug	Dosage Form	Route of Administration
Bevacizumab	vial	intravenous
Irinotecan	vial	intravenous
Fluorouracil (5-FU)	vial	intravenous
Leucovorin (Folinic Acid)	vial	intravenous

FOLFIRI and bevacizumab should be obtained commercially via the site pharmacy. Each site will be responsible for tracking the lot numbers for all FOLFIRI and bevacizumab dispensed.

5.5.5 Packaging and Labeling

Veliparib will be packaged in bottles containing 20 or 44 capsules of 50 mg active or placebo. This will allow for the 2 or 5 days of administration with one additional dose to cover loss, spillage or replacement due to vomiting within 15 minutes. Each bottle label will include all information as required by local regulations and must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

5.5.6 Storage and Disposition

Veliparib or Placebo

Table 10. Study Drug Storage Conditions

Study Drug	Country	Storage Conditions
Veliparib or placebo	All countries, except Australia/New Zealand	Store at 15°C to 25°C (59°F to 77°F)
	Australia/New Zealand	Store below 25°C

All clinical supplies provided by AbbVie must be stored in a secure place at the proper storage conditions as presented in Table 10, until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label.

Storage and Disposition of FOLFIRI and Bevacizumab

Irinotecan, Fluorouracil (5-FU), Leucovorin (Folinic Acid) and Bevacizumab should all be stored per locally approved label or SmPC in the provided cartons to protect from light.

5.5.7 Method of Assigning Subjects to Treatment Groups

All subjects in the study will be randomized using an IRT system. Before the study is initiated, directions for the IRT system will be provided to each site. Subject randomization will be stratified into 4 groups as described in Section 8.3. The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

During randomization, subjects within each of the stratification groups will be randomized in a 1:1 ratio to one of the following protocol therapy groups:

a. Veliparib plus FOLFIRI ± bevacizumab

b. Placebo plus FOLFIRI ± bevacizumab

5.5.8 Selection and Timing of Dose for Each Subject

All randomized subjects will receive 200 mg of veliparib/placebo orally BID on Day –2 through Day 5 of each 14-day cycle. No other doses or schedules of veliparib are being investigated in this study.

5.5.9 Blinding

The Investigator, his or her clinical and research staff, and subjects will remain blinded to each subject's treatment with veliparib/placebo throughout the course of the study. Site pharmacy personnel will be unblinded throughout the study. To monitor patient safety on an ongoing basis, AbbVie study personnel will remain unblinded throughout the study.

AbbVie must be notified before the blind is broken by the Investigator unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.5.10 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense protocol therapy only to subjects enrolled in the study in accordance with the protocol. The protocol therapy must not be used for reasons other than that described in the protocol. Veliparib/placebo should be taken as directed by the Investigator. FOLFIRI and bevacizumab will be administered intravenously by trained site personnel.

Unless otherwise directed by the Investigator, the subject will be considered compliant with all study therapy if at least 80% of the assigned dose of FOLFIRI, bevacizumab

(when used), and veliparib/placebo is taken during a cycle. Compliance below 80% will require counseling of the subject by study site personnel.

Subjects will be instructed to return all veliparib/placebo bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Final Visit. The site staff will document the bottles returned and the number of capsules per bottle on the appropriate form.

Upon completion or termination of the study, all original bottles/cartons containing unused veliparib/placebo (empty containers will be defaced and discarded on site) will be returned to AbbVie according to AbbVie's instructions, or if pre-arranged between the sponsor and site, destruction of used and unused bottles will be performed at the site.

5.5.11 Drug Accountability

The Investigator or his/her designated representative agrees not to supply protocol therapy to any persons not enrolled in the study or not named as a subinvestigator listed on the FDA 1572 or Investigator Information and Agreement (IIA) form.

Veliparib/Placebo

Upon receipt of a shipment of veliparib/placebo, the representative at each site will 1) open and inspect the shipment; 2) verify that the veliparib/placebo has been received intact, in the correct amounts and at the correct address; 3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment; 4) register the shipment as received via the IRT. All veliparib/placebo must be retained in the designated secure area under proper storage conditions. This will be documented by signing and dating the POR or similar document or via direct recording in the IRT.

An overall accountability of veliparib/placebo will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of veliparib/placebo will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy and will include the lot

number, POR number(s), the bottle/kit numbers, and the date study drug was dispensed for each subject.

Upon completion or termination of the study, all original containers (empty or containing unused veliparib/placebo) will be returned to AbbVie according to instructions from AbbVie or if pre-arranged between the sponsor and site, destruction of used and unused study drug in bottles will be performed at the site.

Standard of Care Medicinal Products

The site will record the dose of irinotecan, 5-FU, leucovorin, and bevacizumab given to each subject in the source documents and on the eCRF. As the Investigator will obtain irinotecan, 5-FU, leucovorin, and bevacizumab commercially, site inventory and accountability of irinotecan, 5-FU, leucovorin, and bevacizumab will not be performed, and drug accountability forms will not be provided. However, each site will be responsible for tracking the lot numbers for all irinotecan, 5-FU, leucovorin, and bevacizumab dispensed.

Site pharmacy personnel will document whether the bolus was prepared with or without 5-FU for each subject. It is the site pharmacy personnel's responsibility to ensure this documentation remains confidential and is not shared with any other site staff members.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The FOLFIRI combination is standard first-line treatment for previously untreated metastatic adenocarcinoma of the colon or rectum. Veliparib may have a potential benefit for subjects with mCRC. This randomized, blinded, placebo-controlled study will evaluate the treatment effect due to the addition of veliparib to FOLFIRI ± bevacizumab chemotherapy in subjects with previously untreated metastatic adenocarcinoma of the colon or rectum.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard and validated.

5.6.3 Suitability of Subject Population

Subjects with pathologically documented and previously untreated metastatic adenocarcinoma of the colon or rectum will be selected to participate in this study. The proposed inclusion and exclusion criteria are anticipated to result in a study subject population representative of mCRC who receive systemic therapy according to current practice guidelines.[2]

5.6.4 Selection of Doses in the Study

The initial starting dose of 200 mg BID veliparib in this trial was derived from the results obtained in the Phase 1 dose escalation study (Study M10-977). The maximum dose of veliparib/placebo for any subject in this study is 200 mg BID for 7 of 14 days per cycle. A Phase 1 dose escalation study evaluating veliparib in combination with FOLFIRI found that the 5-FU bolus is not tolerated; therefore, subjects randomized to the veliparib arm will receive modified FOLFIRI without a 5-FU bolus.[17] For subjects randomized to the placebo arm, FOLFIRI will be given as per standard of care in first-line treatment for mCRC per NCCN guidelines, 2014.[2] Should the investigator elect to treat with bevacizumab, it will be given as per standard of care in first-line treatment for mCRC as per NCCN guidelines, 2014.[2]

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the

Investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Appendix E, Appendix F, Appendix G, Appendix H, and Appendix I regarding toxicity management) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and was pre-planned prior to study entry, or performed for curative intent. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed

earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

All protocol-related AEs must be collected from the signing of the study specific informed consent until study drug administration. In addition, adverse events with onset or worsening reported by a subject from the time that the first dose of study drug (veliparib or placebo) is administered until 30 days have elapsed following discontinuation of study drug administration will be considered as treatment-emergent adverse events.

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility, hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.2 Adverse Events Expected Due to mCRC or Progression of mCRC

Events that are clearly consistent with the expected progression of mCRC, including but not limited to tumor pain, bowel obstructions, and constipation should be considered as expected. A list of expected adverse events is presented in Appendix C of the protocol. These adverse events may occur alone or in various combinations and are considered expected adverse events in mCRC subjects.

6.3 Adverse Events Expected Due to Study Related Endpoints

6.3.1 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 6.6) that are more likely related to disease progression will therefore be an expected adverse event and will not be subject to expedited reporting.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.3.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

6.4 Adverse Event Severity

The study Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE Version 4.0.[19]

For adverse events not captured by the NCI CTCAE Version 4.0, the Investigator will use the following definitions to rate the severity of each adverse event:

Mild (Grade 1)	The adverse event is transient and easily tolerated by the subject.
Moderate (Grade 2)	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe (Grade 3 or 4)	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

Death (Grade 5)	The adverse event resulted in death of the subject.

If a reported adverse event increases in severity, the initial adverse event should be given an outcome date and a new adverse event should be reported to reflect the change in severity.

For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated and need to include the new AE serial number.

6.5 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug (for the purpose of this section, protocol therapy is considered veliparib/placebo and FOLFIRI ± bevacizumab, all assessed individually):

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.6 Adverse Event Collection Period

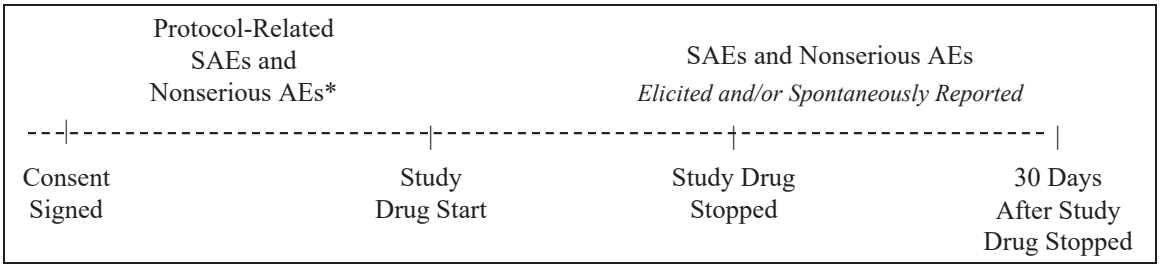
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

In addition, all adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject.

Serious and nonserious adverse events occurring after the study specific informed consent is signed but prior to the initial dose of veliparib/placebo will be collected **only** if they are considered by the Investigator to be causally related to the study-required procedures.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

6.7 Adverse Event Reporting

In the event of a serious adverse event, whether associated with protocol therapy or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the EDC system (RAVE®). Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE® is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical

Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Serious adverse events which are considered expected due to the underlying disease of mCRC as described in Appendix C would not be expedited as individual safety case reports to regulatory authorities.

Email to:	[redacted]
FAX to:	[redacted]

For safety concerns, contact the AbbVie Oncology Safety Management Team at:

[redacted]

For any subject safety concerns, please contact the AbbVie Study Designated Physician listed below:

[redacted]

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie SDP:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for veliparib or Summary of Product Characteristics (SmPC) for irinotecan, 5-FU, and leucovorin.

6.8 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue protocol therapy and must be discontinued from the study. The Investigator must report the positive pregnancy test to the Study Designated Physician listed in protocol Section 6.7 within 1 working day of the site becoming aware of the pregnancy.

All subjects should be informed that contraceptive measures should be taken throughout the study and for 90 days after discontinuing protocol therapy. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. The Investigator must follow the pregnancy to completion and provide an update to AbbVie after delivery.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie contacts. Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study:

Primary Contact: Alternate Contact (Primary):

Alternate Contact (Secondary):

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The data of randomization (enrollment) is defined as the data that the IRT issues a randomization number.

All subjects who are randomized will be included in the efficacy analyses.

All subjects who receive at least one dose of the study drug (veliparib or placebo) will be included in the safety analysis.

8.1.1 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics prior to the initiation of study drug (or randomization for non-treated subjects). Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug.

8.1.1.1 Demographics

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, minimum, maximum, and range. Frequencies and percentages will be computed for the following parameters: gender, race, planned bevacizumab use, geographical region, and ECOG performance status.

8.1.1.2 Medical History

Frequencies and percentages will be computed for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy analysis will be a comparison of progression-free survival (PFS) between veliparib 200 mg BID plus FOLFIRI ± bevacizumab, and placebo for veliparib BID plus FOLFIRI ± bevacizumab.

For a given subject, PFS will be defined as the number of days from the date the subject was randomized to the date the subject experiences an event of disease progression or death, whichever occurs first. All events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. Events of death will be included for subjects who had not experienced an event of disease progression, provided the death occurred within 8 weeks of the last evaluable disease progression assessment. If the subject does not have an event of disease progression and the subject has not died as defined above, the subject's data will be censored at the date of the subject's last evaluable disease progression assessment.

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy analyses comparing the effects of veliparib plus FOLFIRI ± bevacizumab and placebo plus FOLFIRI ± bevacizumab on the following set of endpoints will be performed: overall survival (OS) and objective response rate (ORR).

Time to death (overall survival) for a given subject will be defined as the number of days from the date the subject was randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug. If a subject has not died, the data will be censored at the date last known to be alive.

Objective response rate (ORR) is calculated as the proportion of subjects who have PR or CR based on assessment by RECIST, Version 1.1. Subjects who receive local therapy (surgery, radiation, etc.) will be censored at the time of surgery from subsequent ORR assessments.

8.1.2.3 Tertiary Efficacy Endpoints

Tertiary efficacy analyses comparing the effects of veliparib plus FOLFIRI ± bevacizumab and placebo plus FOLFIRI ± bevacizumab on the following set of endpoints will be performed: duration of overall response (DOR) and changes in ECOG performance status.

Duration of Overall Response (DOR) will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that progressive disease PD is observed. If a subject is still responding then the subject's data will be censored at date of the last available disease progression assessment. For subjects who never experienced CR or PR, the subject's data will not be included in DOR analysis.

ECOG performance status is a scale from 0 to 4 collected at baseline, Day 1 of each cycle and final visit.

8.1.3 Primary Analysis of Efficacy

The progression-free survival distribution will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using a log-rank test stratified by the planned bevacizumab use. A two-sided, stratified log-rank test *P* value will be provided. Median PFS time will be estimated and a 95% confidence

interval for the median PFS time will be presented for each treatment group. A hazard ratio estimate and a 95% confidence interval will be obtained from a proportional hazards regression model.

8.1.4 Secondary Analysis of Efficacy

8.1.4.1 Overall Survival

The distribution of overall survival will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two treatment groups using a log-rank test stratified by the planned bevacizumab use. Median OS time will be estimated and a 95% confidence interval for the median OS time will be presented for each treatment group. A hazard ratio estimate and a 95% confidence interval will be obtained from a proportional hazards regression model.

8.1.4.2 Objective Response Rate

The objective response rate will be estimated and compared between the two treatment groups using a Cochran-Mantel-Haenszel test, stratifying by the planned bevacizumab use. In addition, a 95% confidence interval will be constructed for the estimated proportions.

8.1.4.3 Tertiary Analysis of Efficacy

8.1.4.3.1 ECOG Performance Status

Changes from baseline in ECOG performance status will be summarized using descriptive statistics for each scheduled post-baseline visit and for the final visit. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Changes from baseline to each visit will be compared between the two treatment groups using an analysis of covariance with treatment group as the factor and baseline value as a covariate.

8.1.5 Safety Assessments

The safety of the study regimens will be assessed by evaluating study drug exposure, adverse events, serious adverse events, and all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who were randomized but did not receive study drug (veliparib or placebo) will not be included in the analyses of safety.

8.1.6 Statistical Analyses of Safety

8.1.6.1 Duration of Study Drug

A summary of the number of days and/or cycles subjects were exposed to study drug will be provided.

8.1.6.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug (veliparib or placebo). Analyses will not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events will be coded and summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given NCI CTCAE version 4.0 grade, and relationship to study drug will be provided. Comparisons of the percentages of subjects experiencing an adverse event between the veliparib and placebo study arms will be performed using Fisher's exact test.

8.1.6.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described above in Section 8.1.6.2.

8.1.6.4 Deaths

The number of subject deaths will be summarized 1) for deaths occurring while the subject was still receiving study drug in this study, 2) for deaths occurring off treatment within 30 days after the last dose of study drug, and 3) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.1.6.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of randomized study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. Comparisons of the differences in mean changes from baseline between the veliparib and placebo arms will be made using ANCOVA with treatment group as the factor and baseline as a covariate.

8.1.6.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0 grades, and shifts from baseline NCI CTCAE version 4.0 grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the grade of the last post-baseline measurement collected no more than 30 days after the last dose of study drug. If multiple values are available for a post-baseline measurement, then the value with the highest NCI CTCAE grade will be used in the assessment of shift. Comparisons of the number of subjects experiencing a shift from baseline grades of 0 to 2 or no grade to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 or no grade to final post-baseline grades of 3 to 4 between the veliparib and placebo arms will be performed

using Fisher's exact tests. Additional analyses including all measurements collected, regardless of the number of days after the last dose of study drug, will be performed.

Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.6.7 Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Detailed listings of data for subjects experiencing potentially clinically significant vital sign values according to the AbbVie-defined criteria for vital sign values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.7 Interim Analysis

To ensure subject safety and assess the efficacy of veliparib during the study, AbbVie will perform at least one efficacy and two safety interim analyses. An Internal Monitoring Committee (IMC) will be formed to review the interim data and make recommendations to the conduct of the study. A separate IMC agreement defines the roles and responsibilities of the IMC, including its membership, scope, timing of meetings, and communication plan.

The first safety interim analysis will occur at least 8 – 10 weeks after 20 subjects in the "planned bevacizumab use" group are randomized. All subjects who have received at least 1 dose of protocol therapy prior to the database versioning date will be included in this analysis. The main objective for this early interim assessment will be to evaluate the safety of veliparib when combined with bevacizumab and FOLFIRI, which was not tested during any previous veliparib trials.

A second interim analysis for both efficacy and safety will be conducted at least 8 – 10 weeks after 35 PFS events have occurred. The Internal Monitoring Committee will

review efficacy data to determine the futility of the study. A comprehensive review and assessment of the cumulative safety data will also be undertaken at the same time. The main objective for this interim safety assessment will be to determine if the safety of veliparib in combination with FOLFIRI is sufficient to allow the on-study treatment to continue, or if a modification to the study should be made.

8.2 Determination of Sample Size

A minimum of 70 PFS events was chosen to provide adequate precision in the hazard ratio estimate. Assuming median PFS time of 9.4 months in the FOLFIRI ± bevacizumab arm and 15.7 months in the veliparib plus FOLFIRI ± bevacizumab arm, based on a minimum of 70 PFS events, the expected 95% confidence interval for the estimated hazard ratio would be approximately 0.37 to 0.96. A total of 120 subjects will be enrolled into the study. Assuming a total enrollment period of 12 months, it is anticipated that the study will complete by end of the 22nd month if the true median times for each treatment arm are as assumed above.

8.3 Randomization Methods

An IRT system will be utilized to randomize subjects. Before the study is initiated, directions for the IRT will be provided to each site. The investigational site will contact the IRT on or prior the subject's C1D–2 visit and a unique randomization number will be provided.

Subject randomization will be stratified into 4 groups as follows:

Group	Strat Factor 1	Strat Factor 2
1	North America	Planned Bevacizumab Use
2	North America	No Planned Bevacizumab Use
3	Rest of World	Planned Bevacizumab Use
4	Rest of World	No Planned Bevacizumab Use

During randomization, subjects within each of the 4 stratification groups will be randomized in a 1:1 ratio to either the veliparib 200 mg BID plus FOLFIRI group or the placebo BID plus FOLFIRI group.

The stratification factors used for the randomization should be the last values on or prior to the date of randomization and should be consistent with those on the eCRF.

Randomization will be conducted to ensure that at least 60 subjects are enrolled in both the "planned bevacizumab use" group and "no planned bevacizumab use" group for a total of ~120 subjects.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and

any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record or Investigator binder per local legislation. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called RAVE® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person

performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical

conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of last subject's last survival follow-up contact. The sponsor may also end the study upon confirmation that the primary endpoint was statistically met.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for veliparib (ABT-888) and the product labeling for irinotecan, fluorouracil (5-FU), leucovorin, and bevacizumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer
Protocol Date:	16 July 2015

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		GDSM
		Statistics
		Statistics
		Clinical
		Pharmacokinetics
		Bioanalysis

Appendix C. Adverse Events Expected Due to mCRC or Progression of mCRC

Preferred Term (MedDRA Version 13.1)
Tumor pain
Bowel obstruction
Biliary obstruction/cholestasis
Fatigue
Abdominal pain
Abdominal pain upper
Abdominal pain lower
Anorexia
Nausea
Diarrhea
Constipation
Vomiting
Dyspnea
Pyrexia
Asthenia
Rectal haemorrhage
Abdominal distension
Proctalgia
Intestinal obstruction
Progression of metastatic colon cancer
Progression of metastatic rectal cancer
Metastases to lymph nodes
Metastases to liver
Metastatic pain
Cancer pain
Non-cardiac chest pain

Appendix D. RECIST Version 1.1 for Tumor Response (PFS)

Response criteria will be assessed using RECIST, Version 1.1. Changes in the measurable lesions over the course of therapy must be evaluated using the criteria listed below.

Eligibility

Subjects with measurable disease at baseline can have objective tumor response evaluated by RECIST, Version 1.1. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: Longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.
Special Considerations Regarding Lesion Measurability	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 MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable. Cystic lesions Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. Lesions with prior local treatment Tumor lesions situated in a previously irradiated area, or 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.

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

Methods of Measurement

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie Study Designated Physician.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected 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. 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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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 of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Non-Evaluable (NE):

To be exclusively used for subjects who have undergone surgical resection with curative intent who no longer have a measurable lesion. Subjects who undergo surgical resection will resume protocol therapy and study visits until there is a new lesion (PD).

Progressive Disease (PD):

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD:

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

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Appendix E. Guidelines for Toxicity Management and Dose Reductions or Delays for Protocol Therapy

If a subject experiences adverse events that results in the dose modification (including dose delay, reduction, or discontinuation) of veliparib/placebo, FOLFIRI, or bevacizumab during a cycle, the subject will complete the planned activities of the cycle as scheduled per Table 4 (i.e., vital signs, labs, radiographic tumor assessment, etc.) until resuming protocol therapy.

If a dose interruption is needed, the subject will continue to have study visits as planned; however, PD and/or PK samples will not be collected during this period. Dose interruptions for events that are clearly not related to the protocol therapy (e.g., underlying cancer, planned surgical procedures or acute viral illnesses) should not necessitate a dose reduction. The timing of dose resumption should be at the discretion of the Investigator; however, the primary contact listed in Section 8.0 should be contacted regarding the timing of PD and/or PK sample collection once subjects have resumed dosing.

Subjects can be treated with antibiotic therapy if they develop severe neutropenia. A new cycle of treatment (i.e., Day –2 of the next cycle) may not begin until the ANC is $\geq 1500/mm^3$, the platelet count is $\geq 100{,}000/mm^3$, and any treatment-related GI toxicity has resolved to $\leq$ Grade 1. If the initiation of a new cycle, or therapy during a cycle is delayed for ≥ 4 weeks, Investigators should contact the Study Designated Physician regarding ongoing clinical benefit prior to resumption of protocol therapy.

Dose modifications should be based on laboratory values obtained as described in Section 4.3.1.1. Interval counts (i.e., CBC's done on non-FOLFIRI days) are not determinants of dose reductions unless associated with other issues such as febrile neutropenia.

Dose reductions and delays for veliparib/placebo, FOLFIRI, and bevacizumab toxicity are described in Appendix F, Appendix G, Appendix H, and Appendix I.

Appendix F. Dose Reductions and Delays for Veliparib Toxicity

The following are guidelines for dose reduction, delay and discontinuation of veliparib:

- For any Grade 3 or 4 toxicity attributable to veliparib and not FOLFIRI nor underlying disease.
- Any event of seizure, regardless of grade or attribution, requires interruption of veliparib and discussion with the AbbVie Study Designated Physician regarding the decision to resume treatment.

Veliparib will be held until the toxicity(ies) recovery to ≤ Grade 1 or baseline grade if present at screening. Upon resuming veliparib/placebo treatment, the dose is to be reduced one dose level as shown below.

If a subject begins veliparib/placebo on Day –2 but subsequently experiences an event requiring delay of the FOLFIRI dosing on Day 1, the subject is to stop veliparib/placebo dosing immediately. Upon resolution of the event, the subject may restart the current cycle by repeating Day –2 and Day –1. For such delays, a new veliparib supply will be dispensed to restart the cycle at Day –2.

For the purposes of this study, only three dose reductions of veliparib/placebo are allowed. All dose reductions are permanent. If a dose reduction is required beyond dose level 3, subjects should discontinue all protocol therapy. If an intolerable toxicity does not develop, treatment with additional cycles of protocol therapy may be continued indefinitely as long as subjects continue to experience clinical benefit.

Veliparib Dose Reduction or Delay

Drug	Starting Dose	Level 1 Reduction	Level 2 Reduction	Level 3 Reduction
Veliparib/Placebo	200 mg BID	150 mg BID	100 mg BID	50 mg BID

Appendix G. Dose Reductions and Delays for FOLFIRI Toxicity

Dose modification for the current cycle and reduction for subsequent cycles should be carried out as shown below. Dose adjustments of irinotecan and 5-FU infusion may be made independently based on the specific types of toxicities observed as discussed in Appendix I. For the purposes of this study, only three dose reductions of FOLFIRI are allowed. If a dose reduction is required beyond dose level 3 for irinotecan, discontinue irinotecan use, but continue veliparib/placebo, 5-FU, leucovorin and bevacizumab. If a dose reduction is required beyond dose level 3 for 5-FU, discontinue all protocol therapy.

Note: The 5-FU bolus can only be skipped or discontinued.

FOLFIRI Dose Reductions

Drug*	Starting Dose	Dose Level –1	Dose Level –2	Dose Level –3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	100 mg/m^2
5-FU Infusion	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2	1360 mg/m^2
5-FU Bolus	400 mg/m^2	Discontinued	Discontinued	Discontinued

* Leucovorin is always administered at 400 mg/m^2 IV prior to the 5-FU infusion. If an infusion of 5-FU needs to be skipped, leucovorin must also be skipped.

Appendix H. Dose Reductions and Delays Guidelines for Bevacizumab Toxicity

Bevacizumab is always administered at 5 mg/kg IV. Bevacizumab may be skipped or discontinued, but the dose is not reduced.

Appendix I. Toxicity Management Guidelines for Protocol Therapy

Hematologic Toxicities:

The following dose modifications are recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 of any cycle):

- Grade 2 neutropenia or thrombocytopenia, discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next cycle. For each subsequent cycle, may resume 5-FU infusion and irinotecan at the previous dose levels, provided ANC $\geq$ 1500/µL and platelets $\geq$ 100,000/mm^3.
- Grade 3 or 4 neutropenia or thrombocytopenia, suspend all protocol therapy. If counts recover to ANC $\geq$ 1500/µL and platelets $\geq$ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.
- Febrile neutropenia (defined as ANC < 1000/µL and T $\geq$ 38.5°C), suspend all protocol therapy. If fever resolves, and counts recover to ANC $\geq$ 1500/µL and platelets $\geq$ 75,000/mm^3 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.
- Veliparib may exacerbate neutropenia or thrombocytopenia associated with FOLFIRI. Investigators should consider reducing veliparib/placebo one dose level, as appropriate. Subjects should not receive veliparib while 5-FU infusion and irinotecan are suspended. Skipped doses are not to be made up.
- No bevacizumab dose modifications will be made for hematologic toxicity. Subjects should not receive bevacizumab while 5-FU infusion and irinotecan are suspended. Resume bevacizumab concurrently with FOLFIRI when 5-FU and irinotecan are skipped for hematologic toxicities.

Gastrointestinal Toxicities:

Diarrhea: Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. It is strongly suggested that Atropine, 0.25 – 1.0 mg IV

or SC be used at the time of irinotecan administration to prevent these symptoms. Additional antidiarrheal measures may be used at the discretion of the Investigator. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

Late diarrhea (e.g., developing more than 24 hours after irinotecan) should be managed with loperamide as described below.

The following concomitant medications and/or dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):

Oral fluoroquinolone treatment should be initiated for any of the following:

- Diarrhea persisting for more than 24 hours despite loperamide.
- ANC < 500/μL (even in the absence of diarrhea or fever).
- Fever with diarrhea (even in the absence of neutropenia).
- Antibiotic therapy should also be initiated in patients who are hospitalized with prolonged diarrhea (even in the absence of neutropenia).
- For Grade 2 diarrhea, discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next cycle. For each subsequent cycle, resume 5-FU infusion and irinotecan at the previous dose levels, provided diarrhea has fully resolved.
- For Grade 3 or 4 diarrhea, suspend all protocol therapy. If diarrhea resolves to ≤ Grade 2 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.
- No veliparib/placebo or bevacizumab dose reductions should be made for diarrhea. Subjects should not receive veliparib or bevacizumab while 5-FU infusion and irinotecan are suspended. Skipped doses are not to be made up.

For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, subjects will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of 1) a poorly formed or loose stool or 2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or 3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Subjects may take loperamide 4 mg every 4 hours during the night. The maximum daily dose of loperamide is 16 mg/day. Subjects should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the Investigator. Subjects should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

Mucositis: The following dose modifications are based the grade of mucositis seen on the day of treatment for any day after Day 1 in any cycle.

- For Grade 2 mucositis, may discontinue 5-FU bolus. Reduce 5-FU infusion and irinotecan one dose level for the next cycle. For each subsequent cycle, may resume 5-FU infusion and irinotecan at the previous dose levels, provided mucositis has fully resolved.
- For Grade 3 or 4 mucositis, suspend all protocol therapy. If mucositis resolves to ≤ Grade 2 within 4 weeks, resume protocol therapy with dose reductions as follows: discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level.
- No veliparib/placebo or bevacizumab dose reductions should be made for mucositis. Subjects should not receive veliparib or bevacizumab while 5-FU infusion and irinotecan are suspended. Skipped doses are not to be made up.

Nausea/Vomiting: The following dose modifications are based on the grade of nausea and vomiting occurring during a cycle (i.e., after Day 1 in any cycle).

- For Grade 3 nausea or vomiting, reduce irinotecan one dose level for the next cycle. For each subsequent cycle, may continue irinotecan at previous dose level, provided nausea has resolved ≤ Grade 2.
- For Grade 4 nausea or vomiting, discontinue 5-FU bolus and continue 5-FU infusion and irinotecan at one lower dose level. These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite two treatments with adequate (combination) antiemetic therapy. The use of aprepitant is prohibited for those patients receiving FOLFIRI.
- Veliparib may exacerbate nausea associated with FOLFIRI. Investigators should consider reducing veliparib/placebo one dose level as appropriate.
- No bevacizumab dose modifications will be made for diarrhea, mucositis, nausea, or vomiting. Continue bevacizumab when 5-FU and irinotecan are skipped for these GI toxicities.

Pulmonary Toxicities

- For ≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates, skip bevacizumab until interstitial lung disease is ruled out. Continue irinotecan and 5-FU/leucovorin. Discontinue all protocol therapy if interstitial lung disease is confirmed.
- No veliparib/placebo dose reductions should be made for pulmonary toxicities.

Hypertension

- For hypertension controlled with medication (to < 160/90 mmHg): Continue bevacizumab.
- For persistent or symptomatic hypertension: Skip bevacizumab. If bevacizumab treatment is delayed for more than 4 weeks due to uncontrolled hypertension, discontinue bevacizumab.
- Grade 4 hypertension: Discontinue bevacizumab. Patients who skip or discontinue bevacizumab due to hypertension may continue other protocol therapy.
- No veliparib/placebo dose reductions should be made for hypertension.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS/PRES)

For signs and symptoms suggestive of RPLS (e.g., confusion, headache, seizures, cortical blindness) skip bevacizumab. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, bevacizumab should be permanently discontinued.

If RPLS is ruled out via MRI, the decision on resuming bevacizumab should be based on the nature of the signs/symptoms. For Grade 4 events with likely relationship to bevacizumab, discontinue bevacizumab; for Grade 3 events, bevacizumab may be resumed if toxicities completely resolve within 4 weeks.

Other protocol therapy may be continued at the discretion of the Investigator.

Cardiovascular Toxicities:

Subjects should be carefully monitored for evidence of thromboembolic disease during treatment.

Venous Thrombotic Events

- For Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Skip bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:
  - The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on stable dose of low molecular weight heparin prior to restarting bevacizumab treatment;
  - The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels);
  - The patient must not have had hemorrhagic events while on study.
- For Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of bevacizumab: Discontinue all protocol therapy.

- For symptomatic pulmonary embolism, subjects will discontinue all protocol therapy.

Arterial Thrombotic Events

- For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cardiac ischemia/infarction, discontinue all protocol therapy.
- For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol therapy.

Left Ventricular Dysfunction

- For Grade 3 LV dysfunction, discontinue bevacizumab. Subjects may continue other protocol therapy.
- For Grade 4 LV dysfunction, discontinue all protocol therapy.

Hemorrhage/Bleeding

- For Grade 3 hemorrhage/bleeding, discontinue bevacizumab and skip other protocol therapy; once hemorrhage or bleeding resolves, other protocol therapy may be continued at the treating physician's discretion.
- For Grade 4 hemorrhage/bleeding, discontinue all protocol therapy.

Proteinuria

- For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection or urine protein to creatinine (UPC) ratio. For 2+ proteinuria, the scheduled dose of bevacizumab may be given while awaiting the results of the 24-hour collection or UPC ratio. For > 2+ proteinuria, skip bevacizumab

while awaiting results of the 24-hour urine collection or UPC ratio. Other protocol therapy may be continued.

- If proteinuria is ≥ 2 g/24 hours or UPC ratio ≥ 2.0, skip bevacizumab until urine protein recovers to < 2 g/24 hours or UPC < 2.0, continue other protocol treatment. If bevacizumab is delayed more than 8 weeks due to proteinuria, discontinue bevacizumab.
- If nephrotic syndrome (Grade 4 proteinuria) occurs, discontinue bevacizumab.
- No veliparib/placebo dose reductions should be made for proteinuria.

Wound Dehiscence, GI Perforation, or Intra-Abdominal Fistula

- For wound dehiscence requiring medical or surgical intervention: Discontinue bevacizumab.
- For any grade GI perforation, GI leak, or intra-abdominal fistula: Discontinue bevacizumab.

Hypersensitivity and Infusion Reactions

Note that the NCI CTCAE defines these reactions differently: "Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the CTCAE version 4.0 for a complete list of signs and symptoms of "Cytokine release syndrome/acute infusion reaction;" and see the "Allergy/Immunology" section for a description of hypersensitivity.

Bevacizumab Dose Modifications for Infusion Reactions

The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should

be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated. Patients may receive premedication with diphenhydramine 25 to 50 mg intravenously or orally 30 minutes prior to bevacizumab if they have previously experienced mild infusion reactions. Acetaminophen premedication may also be used.

Dose Modifications for Hypersensitivity Reactions

- For Grade 1 hypersensitivity reactions (transient rash, drug fever < 38°C): Decrease the infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
- For Grade 2 hypersensitivity reactions (urticaria, drug fever ≥ 38°C and/or asymptomatic bronchospasm): Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to institutional policy.
- For Grade 3 or Grade 4 hypersensitivity reactions: Stop the infusion. Discontinue all protocol treatment and notify the Study Designated Physician.

Other Non-Hematologic Toxicities

- For all other ≥ Grade 3 non-hematologic toxicities not described above, hold all protocol therapy and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 within 4 weeks, protocol therapy may be resumed. Discontinue the 5-FU bolus and continue with 5-FU infusion and irinotecan at one lower dose level. Veliparib/placebo may be reduced at the discretion of the Investigator.

Appendix J. Protocol Amendment: List of Changes

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Section 1.2 Synopsis
Subsection Methodology:
Heading "Protocol Therapy"
Fifth and sixth sentence previously read:

Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion); leucovorin 400 mg/m^2 (90 minute infusion); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan (180 mg/m^2); leucovorin 400 mg/m^2 (90 minute infusion); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion) on Day 1 of each 14-day cycle.

Has been changed to read:

Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

Section 1.2 Synopsis
Subsection <u>Diagnosis and Main Criteria for Inclusion/Exclusion:</u>
Heading "Main Exclusion:"
Third bullet previously read:

The last course of adjuvant chemotherapy must have ended > 12 months prior to colorectal cancer recurrence;

Has been changed to read:

The last course of adjuvant or neoadjuvant chemotherapy must have ended > 12 months prior to C1D–2;

Section 1.2 Synopsis
Subsection <u>Diagnosis and Main Criteria for Inclusion/Exclusion:</u>
Heading "Main Exclusion:"
Tenth bullet, third sub-bullet previously read:

Symptomatic congestive heart failure;

Has been changed to read:

Symptomatic congestive heart failure (NYHA Class ≥ II);

Section 1.2 Synopsis
Subsection Reference Therapy:
Previously read:

Reference Therapy:	Irinotecan
Dose:	180 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	Intravenous (IV) over 90 minutes
Reference Therapy:	Leucovorin (Folinic Acid)
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 90 minutes
Reference Therapy:	Flourouracil (5-FU) bolus or saline bolus
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV up to 15 minutes
Reference Therapy:	Flourouracil (5-FU) infusion
Dose:	2400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 46 hours

Has been changed to read:

Reference Therapy:	Irinotecan
Dose:	180 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	Intravenous (IV) over 90 minutes ± 30 minutes
Reference Therapy:	Leucovorin (Folinic Acid)
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 90 minutes ± 30 minutes
Reference Therapy:	Fluorouracil (5-FU) bolus or saline bolus
Dose:	400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV up to 15 minutes
Reference Therapy:	Fluorouracil (5-FU) infusion
Dose:	2400 mg/m^2, Day 1 of each 14-day cycle
Mode of Administration:	IV over 46 hours ± 4 hours
Reference Therapy:	Bevacizumab (at the Investigator's discretion)
Dose:	5 mg/kg
Mode of Administration:	IV immediately preceding FOLFIRI

Section 1.3 List of Abbreviations and Definition of Terms
"IDMC" previously read:

IDMC Independent Data Monitoring Committee

Has been changed to read:

IMC Internal Monitoring Committee

Section 3.8 Clinical Experience
Third paragraph, tenth sentence previously read:

The most commonly reported treatment-emergent Grade 3 or 4 adverse events (rate > 10%) were neutropenia (44 subjects, 47.8%), nausea (35 subjects, 38.0%), diarrhea (31 subjects, 33.7%), fatigue (28 subjects, 30.4%), vomiting (25 subjects, 27.2%), anemia (22 subjects, 23.9%), alopecia (18 subjects, 19.6%), decreased appetite (14 subjects, 15.2%), and stomatitis (11 subjects, 12.0%) and two patients in the veliparib 270 mg BID dose level experienced dose-limiting toxicities (one patient with Grade 3 severe gastritis and Grade 3 vomiting and another patient with Grade 4 neutropenia).

Has been changed to read:

The most commonly reported treatment-emergent Grade 3 or 4 adverse events (rate > 5%) were neutropenia (33 subjects, 35.9%), anemia (9 subjects, 9.8%), diarrhea (5 subjects, 5.4%), dehydration (5 subjects, 5.4%) and hypokalemia (5 subjects, 5.4%). Two patients in the veliparib 270 mg BID dose level experienced dose-limiting toxicities (one patient with Grade 3 severe gastritis and Grade 3 vomiting and another patient with Grade 4 neutropenia).

Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph, fifth and sixth sentence previously read:

Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion); leucovorin 400 mg/m^2 (90 minute infusion); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour

continuous infusion) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan (180 mg/m^2); leucovorin 400 mg/m^2 (90 minute infusion); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion) on Day 1 of each 14-day cycle.

Has been changed to read:

Subjects randomized to the veliparib arm will receive modified FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); saline bolus (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle. Subjects randomized to the placebo arm will receive standard FOLFIRI as irinotecan 180 mg/m^2 (90 minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90 minute infusion ± 30 minutes); 5-FU bolus 400 mg/m^2 (up to 15 minute infusion) immediately followed by 5-FU 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

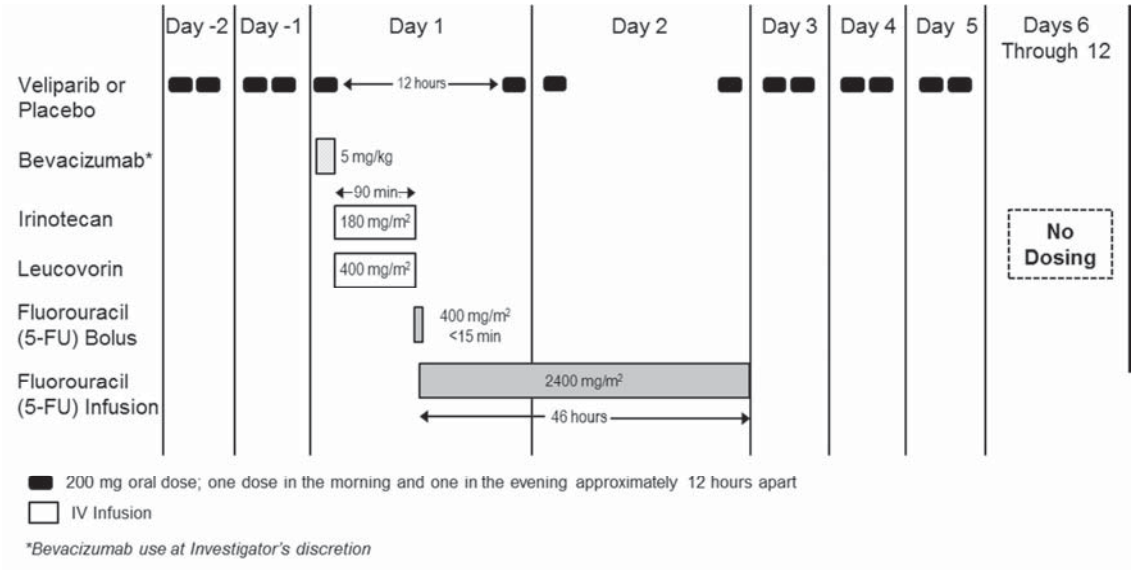
Section 5.1 Overall Study Design and Plan: Description
Eighth paragraph, first sentence previously read:

Sites will begin collecting post-treatment and survival information 4 weeks after the Final Visit.

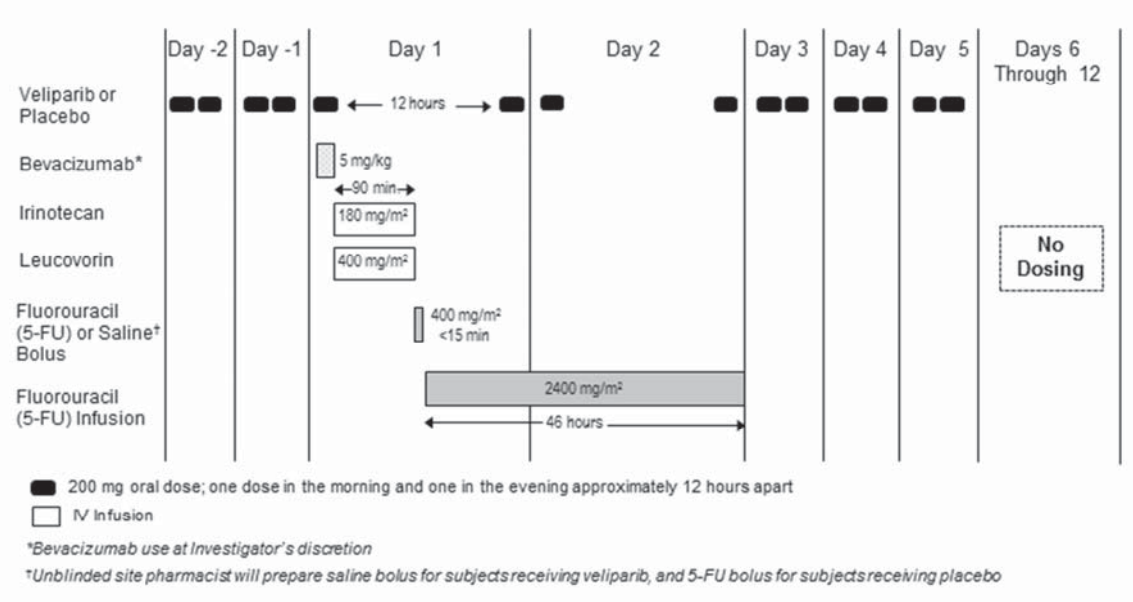
Has been changed to read:

Sites will begin collecting post-treatment and survival information 4 weeks after the last clinical assessment.

Figure 1. Protocol Therapy Dosing Schedule Overview
Previously read:



Has been changed to read:



Section 5.2.2 Exclusion Criteria
Criterion 3 previously read:

The last course of adjuvant chemotherapy must have ended > 12 months prior to colorectal cancer recurrence;

Has been changed to read:

The last course of adjuvant or neoadjuvant chemotherapy must have ended > 12 months prior to C1D–2;

Section 5.2.2 Exclusion Criteria
Criterion 10, third bullet previously read:

Symptomatic congestive heart failure;

Has been changed to read:

Symptomatic congestive heart failure (NYHA Class ≥ II);

Section 5.2.2 Exclusion Criteria
Subsection <u>Rationale for Exclusion Criteria</u>
Previously read:

1 – 4, 8, 11, 13, 16	To select the appropriate subject population with sufficient disease severity for evaluation
5, 6, 9, 10, 12, 14, 15	For the safety of the subjects
17 – 22	For the safety of subjects that receive bevacizumab

Has been changed to read:

1 – 4, 7, 8, 11, 13, 16	To select the appropriate subject population with sufficient disease severity for evaluation
5, 6, 9, 10, 12, 14, 15	For the safety of the subjects
17 – 22	For the safety of subjects that receive bevacizumab

Table 4. Study Assessments
Activity*^ "Physical Exam" previously read:

Activity*^	Screening	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Day 1 of Each Cycle	Every 8 Weeks from C1D1^	Final Visit[a]	30-Day Follow-Up Visit[b]	Survival Period[c]
Physical Exam	X[e]	X[e]	X[e]		X		X		X	X	

Has been changed to read:

Activity*^	Screening	Cycle 1 Day –2	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Day 1 of Each Cycle	Every 8 Weeks from C1D1^	Final Visit[a]	30-Day Follow-Up Visit[b]	Survival Period[c]
Physical Exam	X[e]	X[e]			X		X		X	X	

Table 4. Study Assessments
Table note "e." previously read:

Physical exam not required, if performed within 7 days prior to C1D–2. Height is only measured at Screening.

Has been changed to read:

Height is only measured at Screening. Physical exam is not required on C1D–2 if one has been performed within the last 7 days.

Table 6. Schedule of Pharmacogenetic (PG) and Pharmacodynamic (PD) Assessments
Activity "Tissue Sample Collection" previously read:

Activity	Visit Schedule	Before Drug Administration	Sampling Plan Specimen Matrix
Tissue Sample Collection	Screening[b,d]		Archived FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)

Has been changed to read:

Activity	Visit Schedule	Before Drug Administration	Sampling Plan Specimen Matrix
Tissue Sample Collection	Screening[d]		Archived FFPE tissue blocks (Room Temperature or Refrigerated-FFPE)

Section 5.3.1.1 Study Procedures
Last paragraph, first sentence previously read:

For all study procedures: The study procedures outlined in this protocol are recommendations based on routine safety assessments required during chemotherapy + veliparib administration.

Has been changed to read:

For all study procedures: The study procedures outlined in this protocol are recommendations based on routine safety assessments required during chemotherapy and veliparib administration.

Section 5.3.1.1 Study Procedures
Subsection Medical History
Fifth, sixth and seventh bullet previously read:

- RAS status;
- BRAF status;
- Microsatellite instability (MSI) status.

Has been changed to read:

- RAS status (if known);
- BRAF status (if known);
- Microsatellite instability (MSI) status (if known).

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Third paragraph, first sentence previously read:

A local reference laboratory may perform chemistry, hematology, coagulation, and urinalysis tests for immediate subject management (i.e., emergent situations); however, split or concurrent samples *must* be drawn and sent to the central laboratory for analysis.

Has been changed to read:

A local reference laboratory may perform chemistry, hematology, coagulation, and urinalysis tests for immediate subject management (i.e., emergent situations); however, split or concurrent samples *must* be drawn and sent to the central laboratory for analysis.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Last paragraph previously read:

If there is a discrepancy between the local and central labs, the site must enter the relevant local labs that were used for eligibility or treatment decisions on the appropriate eCRF.

Has been changed to read:

If there is a discrepancy between the local and central labs, the site must enter the relevant local labs that were used for treatment decisions on the appropriate eCRF.

Table 7. Clinical Laboratory Tests
Column "Clinical Chemistry,""Inorganic phosphorus" previously read:

Inorganic phosphorus

Has been changed to read:

Inorganic phosphate

Table 7. Clinical Laboratory Tests
Column "Clinical Chemistry,""Sodium Bicarbonate" previously read:

Sodium Bicarbonate

Has been changed to read:

Bicarbonate/CO^2

Section 5.3.2.1 Blood Samples for Pharmacokinetic Analysis
Section Veliparib Pharmacokinetic Specimen Collection
First paragraph, first and second sentence previously read:

The date and time of sample collection and the date and time of the dose of veliparib will be captured on the eCRF. Blood samples (3 mL) will be collected by venipuncture intoevacuated potassium (K_2) EDTA tubes per Table 5.

Has been changed to read:

The date and time of each blood sample collection will be recorded. The date and time of the veliparib/placebo dose on PK sampling days (refer to Table 5) and the date and time of the two doses of veliparib/placebo prior to PK sampling on C2D1 and C3D1 will be captured on the eCRF.

Section 5.3.2.2 Measurement Methods
Last sentence previously read:

Additionally, veliparib metabolite(s) concentrations in plasma samples may be determined using a non-GLP or a validated assay.

Has been changed to read:

Additionally, veliparib metabolite(s) concentrations in plasma samples may be determined using a non-validated or a validated assay.

Section 5.3.2.3 Blood Samples for Pharmacogenetic Analysis
Second paragraph, first sentence previously read:

The sample collection tubes will minimally be labeled with "PG-DNA," protocol number, subject number and visit.

Has been changed to read:

The sample collection tubes will minimally be labeled with "PG-DNA blood," protocol number, subject number and visit.

Section 5.3.7 Pharmacodynamic Variables
Fourth paragraph previously read:

Samples collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study. Additionally, the samples may be anonymized and used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to

protect confidentiality. The samples will be retained while research on veliparib (or drugs of this class) continues for up to but no longer than 20 years.

Has been changed to read:

AbbVie (or people or companies working with AbbVie) will store and analyze the samples in a secure space with adequate measures to protect confidentiality. Samples will be retained up to 20 years (or per local legal requirement) while research on veliparib (or drugs of this class) or colorectal cancer (or related conditions) continues.

Section 5.4 Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits
Second paragraph previously read:

Additionally, in the event a subject withdraws from the study, pharmacodynamic samples stored for long term biomarker research (no more than 20 years) will also be destroyed. In the event that destruction is not possible, they will no longer be linked to the subject. If the subject changes his/her consent and the samples have already been tested, those results will still remain part of the overall research data. In the event of a subject's death or loss of competence, the samples and data will continue to be part of AbbVie's research but will not be stored more than 20 years.

Has been changed to read:

In the event a subject withdraws consent from participating in the study, stored pharmacodynamic samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research of samples, the subject may request for samples to be withdrawn. Once AbbVie receives the request, remaining samples will be destroyed unless the FDA requires AbbVie to keep the samples. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

Section 5.4.5 Timing and Collection of Survival and Post-Treatment Cancer Information
First paragraph, second sentence previously read:

Sites will collect survival information and post-treatment cancer information beginning 4 weeks after the last study visit and continuing every 4 weeks for 1 year, then every 8 weeks for up to 2 additional years or until the endpoint of death.

Has been changed to read:

Sites will collect survival information and post-treatment cancer information beginning 4 weeks after the last clinical assessment and continuing every 4 weeks for 1 year, then every 8 weeks for up to 2 additional years or until the endpoint of death.

Section 5.5.1 Protocol Therapy Administered
Subsection Dispensing Protocol Therapy
Add: new fourth paragraph

Sites may calculate body surface area (BSA) per local treatment practice. Bevacizumab and FOLFIRI doses should be calculated based on the weight measurement obtained at C1D1. Subsequent bevacizumab and FOLFIRI doses must be recalculated if a subject's body weight increases or decreases by more than 10%.

Section 5.5.1 Protocol Therapy Administered
Subsection Administration of Irinotecan
First sentence previously read:

For the purposes of this protocol, irinotecan 180 mg/m^2 will be administered as a 90 minute IV infusion on Day 1 of each 14-day cycle.

Has been changed to read:

For the purposes of this protocol, irinotecan 180 mg/m^2 will be administered as a 90 minute (± 30 minutes) IV infusion on Day 1 of each 14-day cycle.

Section 5.5.1 Protocol Therapy Administered
Subsection <u>Administration of Leucovorin</u>
First sentence previously read:

For the purposes of this protocol, leucovorin 400 mg/m^2 will be administered as a 90 minute IV infusion concurrent with irinotecan on Day 1 of each 14-day cycle.

Has been changed to read:

For the purposes of this protocol, leucovorin 400 mg/m^2 will be administered as a 90 minute (± 30 minutes) IV infusion concurrent with irinotecan on Day 1 of each 14-day cycle. Irinotecan and leucovorin may be administered sequentially in accordance with local practice.

Section 5.5.1 Protocol Therapy Administered
Subsection <u>Administration of Fluorouracil (5-FU) Infusion</u>
First sentence previously read:

For the purposes of this protocol, 5-FU 2400 mg/m^2 will be administered as a 46-hour IV infusion on Day 1 of each 14-day cycle.

Has been changed to read:

For the purposes of this protocol, 5-FU 2400 mg/m^2 will be administered as a 46-hour (± 4 hours) IV infusion on Day 1 of each 14-day cycle.

Section 5.5.1 Protocol Therapy Administered
Subsection <u>Administration of Bevacizumab</u>
Last sentence previously read:

The initial dose of bevacizumab should be given over 90 minutes, second dose over 60 minutes, and all subsequent doses over 30 minutes if prior infusions are tolerated without infusion associated adverse events.

Has been changed to read:

The initial dose of bevacizumab should be given over 90 minutes (± 30 minutes), second dose over 60 minutes (± 20 minutes), and all subsequent doses over 30 minutes (± 10 minutes) if prior infusions are tolerated without infusion associated adverse events.

Section 5.5.1 Protocol Therapy Administered
Subsection Order of Administration
Add: new second paragraph

Irinotecan and leucovorin may be administered sequentially in accordance with local treatment practice.

Section 5.5.9 Blinding
First paragraph, last sentence previously read:

To facilitate preplanned interim analyses of safety and efficacy data, AbbVie study personnel will remain unblinded throughout the study.

Has been changed to read:

To monitor patient safety on an ongoing basis, AbbVie study personnel will remain unblinded throughout the study.

Section 6.7 Adverse Event Reporting
First paragraph, last sentence previously read:

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE® is not operable should use the SAE Non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Has been changed to read:

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE® is not operable should be documented on the SAE Non-CRF forms and emailed

(preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Section 6.7 Adverse Event Reporting
Fax and email information following second paragraph previously read:

FAX to:	[redacted]
Email to:	[redacted]

Has been changed to read:

Email to:	[redacted]
FAX to:	[redacted]

Section 6.7 Adverse Event Reporting
Fourth paragraph previously read:

For any subject safety concerns, please contact the AbbVie Study Designated Physician listed below:

[redacted]

Has been changed to read:

Section 6.7 Adverse Event Reporting
Fifth paragraph previously read:

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Has been changed to read:

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie SDP:

Section 7.0 Protocol Deviations
First paragraph, first sentence previously read:

AbbVie does not allow intentional/prospective deviations from the protocol.

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects.

Section 7.0 Protocol Deviations
"Primary Contact:" previously read:

Primary Contact:

Primary Contact:

Has been changed to read:

Primary Contact:

Section 7.0 Protocol Deviations
"Alternate Contact (Secondary)" previously read:

Has been changed to read:

Section 8.1.7 Interim Analysis
Previously read:

To ensure subject safety and assess the efficacy of veliparib during the study, AbbVie will perform at least two efficacy and two safety interim analyses.

The two efficacy interim analyses will occur when approximately 25 and 50 PFS events are accrued.

The first safety interim analysis will occur approximately 2 weeks after 10 subjects stratified to the "planned bevacizumab use" group are randomized to the veliparib arm.

The second safety interim analysis will occur at the same time as the first efficacy interim analysis after approximately 107 subjects have completed the first cycle of protocol therapy.

Has been changed to read:

To ensure subject safety and assess the efficacy of veliparib during the study, AbbVie will perform at least one efficacy and two safety interim analyses. An Internal Monitoring Committee (IMC) will be formed to review the interim data and make recommendations to the conduct of the study. A separate IMC agreement defines the roles and responsibilities of the IMC, including its membership, scope, timing of meetings, and communication plan.

The first safety interim analysis will occur at least 8 – 10 weeks after 20 subjects in the "planned bevacizumab use" group are randomized. All subjects who have received at least 1 dose of protocol therapy prior to the database versioning date will be included in this analysis. The main objective for this early interim assessment will be to evaluate the safety of veliparib when combined with bevacizumab and FOLFIRI, which was not tested during any previous veliparib trials.

A second interim analysis for both efficacy and safety will be conducted at least 8 – 10 weeks after 35 PFS events have occurred. The Internal Monitoring Committee will review efficacy data to determine the futility of the study. A comprehensive review and assessment of the cumulative safety data will also be undertaken at the same time. The main objective for this interim safety assessment will be to determine if the safety of veliparib in combination with FOLFIRI is sufficient to allow the on-study treatment to continue, or if a modification to the study should be made.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		GDSM
		Statistics
		Statistics
		Clinical
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		GDSM
		Statistics
		Statistics
		Clinical
		Pharmacokinetics
		Bioanalysis

Appendix I. Toxicity Management Guidelines for Protocol Therapy
Subsection <u>Hematologic Toxicities:</u>
First paragraph previously read:

The following dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):

Has been changed to read:

The following dose modifications are recommended for the next treatment cycle based on unresolved toxicity experienced during a previous cycle (i.e., after Day 1 of any cycle):

Appendix I. Toxicity Management Guidelines for Protocol Therapy
Subsection Gastrointestinal Toxicities:
Third paragraph previously read:

The following dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):

Has been changed to read:

The following concomitant medications and/or dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):

Appendix I. Toxicity Management Guidelines for Protocol Therapy
Subsection Pulmonary Toxicities
First bullet, second sentence previously read:

Continue 5-FU.

Has been changed to read:

Continue irinotecan and 5-FU/leucovorin.

Appendix I. Toxicity Management Guidelines for Protocol Therapy
Subsection Posterior Leukoencephalopathy Syndrome (RPLS)
Subsection title previously read:

Posterior Leukoencephalopathy Syndrome (RPLS)

Has been changed to read:

Reversible Posterior Leukoencephalopathy Syndrome (RPLS/PRES)

Document Approval

Study M14217 - Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer - Amendment 2 - EudraCT 2014-002866-65 - 16Jul2015

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Signed by:	Date:	Meaning Of Signature:
[redacted]	17-Jul-2015 01:06:45 PM	Approver
	17-Jul-2015 01:37:37 PM	Approver
	17-Jul-2015 01:53:43 PM	Approver
	17-Jul-2015 03:08:38 PM	Approver
	17-Jul-2015 05:54:57 PM	Approver
	17-Jul-2015 09:24:29 PM	Approver
	18-Jul-2015 01:31:37 AM	Approver
	20-Jul-2015 01:42:21 AM	Author