A Phase II, randomized, double-blind, study of the use of Rucaparib vs. placebo maintenance therapy in metastatic and recurrent endometrial cancer

Protocol Number:	338-IIT-088/COMIRB #
Principal Investigator:	Bradley Robert Corr, MD Saketh Ram Guntupalli, MD
Coordinating Center and Lead Principal Investigator:	University of Colorado Denver Bradley Robert Corr, MD
Funded by:	Clovis Oncology
Version Date:	09 JUN 2021

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Bradley Robert Corr, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signed: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
ADP	Adenosine Diphosphate
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AP	Cisplatin + Adriamycin
AST	Aspartate Transaminase
BID	Twice a day
BRCA	Breast Cancer
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete blood Count
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CO	Colorado
CO2	Carbon Dioxide
COIC	Office of Regulatory Compliance Conflicts of Interest and Commitment Management
Cr	Creatinine
CR	Complete Response
CT	Computerized Tomography
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C19	Cytochrome P450 2C19
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450, family 3, subfamily A
DCC	Data Coordinating Center
dL	Deciliter
DNA	Deoxyribonucleic acid
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practice

GCSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GOG	Gynecologic Oncology Group
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
HR	Homologous Recombination
HRD	Homologous Recombination Deficiency
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDS	Investigational Drug Service
IIT	Investigator-Initiated Trial
IEC	Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IT	Information Technology
LDL	Low Density Lipoprotein
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndrome
mg	Milligram
mL	Milliliter
MMR	Mismatch Repair
MSI	Microsatellite Instability
mTOR	Mechanistic Target of Rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH IC	National Institute of Health Institute and Centers
NRG	National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG
NSAE	Non-Serious Adverse Event
OHRP	Office of Human Research Protection
ORR	Overall Response Rate
OS	Overall Survival
PA	Pennsylvania
PARP	Polymerase
PD	Progressive Disease
PD1	Programmed Death 1
PIS	Patient Information Sheet
PFS	Progression free survival
PI	Principal Investigator
PIK3CA	Phosphatidylinositol 3-kinase
PO	by mouth

PR	Partial Response
PTEN	Phosphatase and Tensin homolog
QD	once a day
QC	Quality Control
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
SOP	Standard Operating Procedure
TAP	Cisplatin + Adriamycin + Paclitaxel
TIA	Transient Ischemic Attack
UAE	Unanticipated Event
UAP	Unanticipated Problem
UCCC	University of Colorado Cancer Center
UCD	University of Colorado Denver
µL	Microliter
ULN	Upper Limit of Normal
US	United States
VLDL	Very low-density lipoprotein
WBC	White Blood Cells

PROTOCOL SUMMARY / SYNOPSIS

Protocol Title: *A Phase II, randomized, double-blind, study of the use of Rucaparib vs. placebo maintenance therapy in metastatic and recurrent endometrial cancer*

Objectives:

- ***Primary Objective:***
  1. *To measure progression free survival (PFS) with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy.*

- ***Secondary Objectives:***
  1. *To measure overall survival (OS) with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy.*
  2. *To determine the efficacy with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy as measured by overall response rate (ORR) in patients with measurable disease.*
  3. *Safety and tolerability. Safety endpoints including incidence and severity of adverse events and significant laboratory abnormalities.*

- ***Tertiary/Exploratory:***
  1. *To preliminarily assess the efficacy with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy in relation to HRD, BRCA, PTEN, PIK3CA and AKT.*

Endpoint:

- ***Primary Endpoint:***
  Progression free survival (PFS)

- ***Secondary Endpoints:***
  Overall Survival (OS)
  Overall Response rate (ORR)
  Toxicity

- ***Tertiary/exploratory:***
  Disease response for molecular measures (BRCA, HRD, PTEN, PIK3CA, AKT)

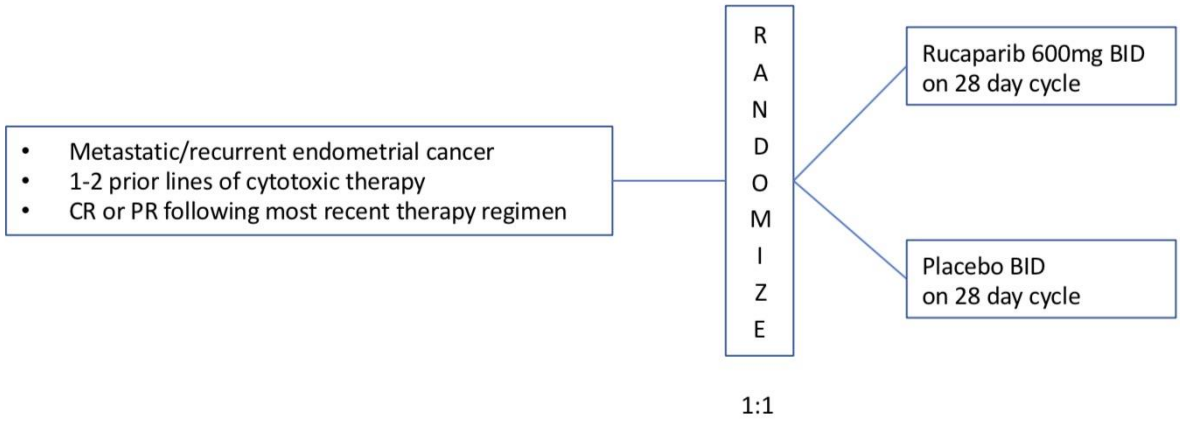
Population:

- ***Sample size***
  - *Maximum number of participants that can be enrolled is 138*
  - *Minimum number of participants to be enrolled 123*

- ***Gender*** *Female*
- ***Age Range*** *18-89*
- ***Demographic group*** *Patients with a primary Stage III/IV or recurrent endometrial cancer whom have received at least one prior chemotherapy regimen and no more than two prior cytotoxic regimens (including hormonal therapy)*
- ***General health status*** ECOG performance status of 0, 1 or 2
- ***Geographic location*** *Denver, CO and Philadelphia, PA; USA*

Phase:	*II*
Number of Participating Sites enrolling participants:	*Total 4 sites*
Description of Study Agent:	*Rucaparib (Rubraca®)*
Study Duration:	*24 months post treatment follow-up for an estimated total study duration of 48 months*

SCHEMATIC OF STUDY DESIGN



1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on a **Protocol Contact List** form, incorporated herein by reference.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Metastatic and recurrent endometrial cancer often carries a dismal long term prognosis with response rates of active chemotherapy or hormonal agents ranging between 20 to 35% [1]. While the search for curative agents is always a goal, maintenance therapy to prolong progression free survival (PFS) would have significant impact on patient care. Currently median PFS in metastatic and recurrent endometrial cancer after first line chemotherapy in large phase III trials has been reported as 8.3 months in GOG 177 [1] and 14 months in GOG 209 [2]. Median overall survival (OS) in this patient population is 32 months as reported in GOG 209 [2]. In response to poor responses from known chemotherapy agents, targeted therapy has been the next logical line of research.

PARP inhibitors are a newer drug class in gynecologic malignancy that have three separate drugs currently FDA approved in recurrent ovarian cancer, Olaparib, Rucaparib and Niraparib. Rucaparib has two approved indications; 1) for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies, and 2) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. PARP inhibition's mechanism of action for cell death works by inhibiting single-strand DNA break repair by blocking the base excision repair pathway which ultimately leads to increased double-strand DNA breaks increasing cell death [3]. The increase in double-strand DNA breaks is also the mechanism for effectiveness of PARP inhibitors in BRCA positive and homologous repair deficient (HRD) patients seen in a multitude of trials in recurrent ovarian cancer [4-8]. The BRCA tumor suppressor gene and HRD patients are deficient in the homolgous repair double-strand DNA repair mechanism, leading to cell death via the principle of synthetic lethality of both single-strand base excision repair deficiency by PARP inhibition and HR repair deficiency by BRCA/HRD [9].

PARP inhibition for maintanaince therapy of recurrent ovarian cancer was first FDA approved for Olaparib based on 4 month PFS benefit seen in a trial known as Study 19 [Ledermann, 2012 #1646]. Most recently Rucaparib has also been approved by the FDA for maintanaince therapy in recurrent ovarian cancer patients based on the results of the ARIEL 3 trial in which a PFS improvement of 11months was seen in BRCA positive patients, 8 months in HRD patients, and 5 months in a separate intent to treat population [Coleman, 2017 #1655]. Rucaparib has been approved for maintanaince therapy in the recurrent setting, as well as third line therapy, with a

standard dosing regimen of 600mg BID based on a multitude of clinical trials that can be referenced in Table 1 of the investigators brochure.

In the search for targeted therapy in the recurrent endometrial cancer patient population, promising pre-clinical data is emerging for the most prevalent genetic alterations in endometrial cancer. Loss of function of the tumor suppressor gene PTEN has been demonstrated in greater than 80% of endometrioid endometrial cancers [2]. PTEN loss of function is well known to lead to activation of the PI3K-AKT-mTOR pathway but has also been shown to lead to defects in homologous recombination (HR) DNA repair of double strand breaks [10]. Based on this mechanism, in vitro data on endometrial cancer cell lines has demonstrated sensitivity to PARP inhibitors. Dedes, et al. have demonstrated that PTEN loss of function is associated with sensitivity to PARP inhibitors and lack of HR DNA repair, PTEN silencing leads to decreased RAD51 foci formation and sensitivity to PARP inhibition, and that the sensitivity of PARP inhibition in PTEN loss of function is independent of microsatellite instability (MSI) [11]. A case report of the use a PARP inhibitor in a PTEN-deficient endometrioid endometrial cancer demonstrated a significant disease response to therapy in a multi-recurrent patient who eventually recurred after 8 months of PARP inhibitor therapy and survived an additional 10 months after progression [12]. PARP inhibitors have shown significant responses in BRCA mutated breast and ovarian cancers, but early data is leading to potential clinical benefit in endometrial cancer patients from genetic mutations variant from BRCA.

In addition to the potential benefit of PTEN deficient endometrial cancers, there may also prove a benefit in a variety of endometrial cancer histologies. Ossovskaya et al. demonstrated a significant expression of PARP in uterine carcinosarcomas [13]. Intuitively this tumor type has high probability of responding to PARP inhibition as the epithelial component of these tumors is often serous which is the major tumor responder in HRD ovarian cancers. Furthermore, Ghabreau et al. demonstrated a correlation between PARP-1 and progesterone receptor expression implying a potential role in PARP-1 expression in non endometrioid endometrial cancer formation [14].

As this therapy has proven efficacy in maintanaince therapy in the recurrent ovarian cancer population, based on the above preclinical data and mechanisms we believe there is potential benefit of maintanaince therapy in the recurrent endometrial cancer population as well.

2.2 RATIONALE/HYPOTHESIS

The study population includes patients with stage III, stage IV, or recurrent endometrial cancer. This population is considered higher risk for progression and has an overall poor prognosis compared to early stage disease. Historically, evaluation of this identical patient population has taken place in both GOG 177 and GOG 209 when looking at adjuvant chemotherapy regimens. GOG 177 evaluated the use of cisplatin and doxorubicin with or without paclitaxel (AP vs TAP)

[1]. TAP therapy was superior with more side effects but overall response rate was 57% and these patients had a PFS of 8.3 months and an OS of 15.1 months. Complete response with TAP therapy was only 22%. GOG 209 evaluated cisplatin, doxorubicin and paclitaxel vs. carboplatin and paclitaxel [15]. Interim analysis of these patients demonstrated non-inferiority of carboplatin and paclitaxel with a PFS of 14 months and a OS of 32 months. Variation in the PFS in the same patient population has been attributed to the fact that GOG 177 inclusion criteria required measureable disease while GOG 209 did not. GOG 209 data has not been fully matured only reported on as interim analysis abstract form to date and therefore this study estimates PFS of this patient population at 8 months based on the best fully published phase III data. Using the existing literature of PARP inhibitor use in maintenance ovarian cancer we expect a PFS improvement of at least 4 months with maintenance therapy [4-6]. Second line chemotherapy for endometrial cancer has extremely low response rates of 9-26% [16]. Extending PFS through the use of maintenance therapy would have significant impact on this patient population.

We expect the majority of patients enrolled on this trial will be those with stage III/IV disease who received a combination of surgery, radiation and chemotherapy consisting of carboplatin and paclitaxel based on GOG 209 and national practice patterns. Standard practice patterns are for patients to receive 6 cycles of carboplatin and taxol for front line therapy though rarely patients do receive fewer or more cycles of therapy. Common reasons for patients to receive fewer lines of therapy would be progression or intolerance of therapy. Common reason for patients to receive more lines of therapy would be partial response after 6 cycles and expected further clinical benefit. Therapy beyond 8 cycles with platinum based therapy is uncommon as platinum reactions typically occur after 8 cycles. As this study aims to evaluate maintanaince therapy we attempt to control for variations in amount of prior chemotherapy regimen received affecting response rates by incorporating this factor into our inclusion criteria. Furthermore, as it is known that serous histology tumors are more aggressive with worse outcomes compared to endometrioid tumor types we plan to stratify on histology to ensure this does not affect our data for either arm of the study. We also plan to stratify on number of prior lines of therapy, 1 vs 2, to ensure PFS data is not affected by one arm weighted with more heavily treated patients. This study is limited to 2 prior lines of therapy as significant clinical benefit in more heavily treated patient population is unlikely to be seen as well as PFS and OS data in patient populations beyond 2 lines is limited and expected to be low.

There is currently no FDA approved therapy for second line treatment of endometrial cancer and NCCN guidelines incorporate a long list of optional therapies based on extensive evaluation of viable chemotherapy regimens. There is no standard of care for this patient population but based on response rates, Adriamycin is considered the most efficacious and is the most common next line of therapy. Limiting the acceptable number of prior lines of therapy, we would expect that the majority of recurrent patients would have received Adriamycin, Doxil, or the newly approved Pembrolizumab if MMR deficient.

Pembrolizumab was recently approved for treatment of adult or pediatric patients with solid tumor that have progressed following prior treatment and have unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient tumors. Previous data from GOG210 demonstrate rates of MMR deficiency as high as 38% of all endometrial cancers, though clinical estimates are closer to a rate of 25% [Goodfellow, 2015 #1675]. There is currently no published data comparing use of any immunotherapy to other second or first line therapy options in recurrent endometrial cancer. We do not believe there is any significant impact of MMR status on this study as there is no known association of PARP inhibition to MMR status, and as described above in preclinical data, MSI status was not associated with PARP sensitivity. For this reason the prior use of Pembrolizumab is acceptable as a prior line of therapy and we expect patients who have received 2 prior lines of who are MMR deficient to have received this therapy.

It is our hypothesis that PARP inhibition will have therapeutic benefit to the metastatic and recurrent endometrial cancer patient population. We aim to demonstrate efficacy in terms of PFS and specifically hope to correlate with common mutational status.

Hypothesis: *We hypothesize that the use of PARP inhibitor maintenance therapy will improve PFS compared to placebo in patients with recurrent or metastatic endometrial cancer who have completed standard first line chemotherapy.*

2.3 POTENTIAL RISKS AND BENEFITS

Synthetic lethality has been exploited in several clinical studies with an oral PARP inhibitor in patients with BRCA-deficient tumor types. These studies evaluated the efficacy of continuous oral dosing of olaparib in women with gBRCA1 or gBRCA2 mutations, and either recurrent ovarian cancer or advanced breast cancer. [17] In these patients, who had received a median of 3 prior chemotherapy regimens, encouraging overall response rates of 33% and 41%, respectively, were observed in patients with a gBRCA mutation. A response rate of 24% was observed in ovarian cancer patients without evidence of a gBRCA mutation. [18] Activity in HGSOC has also been observed with switch maintenance therapy following response to platinum-based chemotherapy. [4, 19] Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median progression-free survival (PFS) (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio of 0.35 (95% confidence interval [CI], 0.25-0.49). [4] Patients with a BRCA mutation derived the most benefit (median PFS 11.2 vs. 4.3 months; hazard ratio, 0.18; 95% CI 0.11-0.31; $p < 0.00001$). [19] In this study, the outcomes of somatic BRCA (sBRCA) mutant + gBRCA mutant patients were the same as gBRCA mutant patients alone, suggesting that it is appropriate to not differentiate between germline and somatic mutations. Patients without a BRCA

mutation also experienced significant benefit from treatment with olaparib (hazard ratio, 0.53; 95% CI 0.33-0.84; p = 0.007). [19]

Based on clinical data of olaparib as treatment for mCRPC patients with predicted loss-of-function alterations in HRR genes such as BRCA1/2 and ATM, [20] rucaparib may also be a compelling therapy for the treatment of patients with this disease. A response rate of 88% (14 of 16 patients) was reported in mCRPC patients who received olaparib and in whom next generation sequencing (NGS) identified homozygous deletions, deleterious mutations, or both in DNA-repair genes, including BRCA1/2, ATM, Fanconi's anemia genes, and checkpoint kinase 2 (CHEK2). Taken together, nonclinical and clinical data indicate that benefit from PARP inhibitor treatment may extend beyond patients with BRCA mutations and support the investigation of PARP inhibitors in a broader group of patients with HRD. Currently, Rucaparib is FDA approved as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.

2.3.1 KNOWN POTENTIAL RISKS

Reference safety information of Rucaparib is available in the Investigators Brochure version 10.0 Section 6.6 and Table 19. Adverse drug reactions presented in the investigators brochure have been extracted from pooled safety data from 917 patients treated with rucaparib in either placebo-controlled Study CO-338-014 (ARIEL3) or one of two open-label, single-arm trials (Studies CO-338-010 and CO-338-017 [ARIEL2]). All 917 patients had either epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and initated rucaparib at a dose of 600 mg BID. The safety profiles were comparable across the 3 studies.

2.3.2 KNOWN POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: Participants will be helping study a maintenance therapy for women with endometrial cancer. Rucaparib has shown success in increasing progression free survival in women with ovarian cancer. Currently there is not an FDA approved maintenance therapy for women with recurrent and/or metastatic endometrial cancer.
- To Society: Rucaparib has proven both safety and efficacy in improving the progression free interval for women with ovarian cancer. Results from this study will support future changes to NCI guidelines in this patient population and future phase III studies.

- Justify the importance of the knowledge gained: Maintenance therapy prolongs a patient's time before recurrence and reduces exposure to cytotoxic chemotherapy agents. This study will provide preliminary efficacy data and genetic response for treating women with recurrent/metastatic endometrial cancer.

3 OBJECTIVES AND PURPOSE

Primary objective: To measure progression free survival (PFS) with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy.

Secondary objectives:

1. To measure overall survival (OS) with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy.
2. To determine the efficacy with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy as measured by overall response rate (ORR) in patients with measurable disease.
3. Safety and tolerability. Safety endpoints including incidence and severity of adverse events and significant laboratory abnormalities.

Tertiary/Exploratory objectives:

1. To preliminarily assess the efficacy with the use of Rucaparib compared to placebo in women with recurrent or metastatic endometrial cancer after first line chemotherapy in relation to HRD, BRCA, PTEN, PIK3CA and AKT.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a phase II, randomized, double-blind, trial for the use of Rucaparib as maintenance therapy in metastatic and recurrent endometrial cancer. Eligible patients will have received 1 to 2 prior lines of cytotoxic therapy and surgery or radiation, if appropriate, prior to randomization. At completion of cytotoxic therapy patients who have demonstrated complete response or partial response will be eligible for randomization. Response to prior line of therapy will be classified based on RECIST 1.1 criteria. Patients with no RECIST 1.1 measurable disease at baseline scan will be considered complete response (CR) from prior therapy. Patients with RECIST 1.1 measurable disease will be compared to prior available imaging to categorize as partial response,

progressive or stable disease related to that line of therapy. If no comparable prior imaging is available for comparison patient will be included at investigator's discretion for progressive disease and categorized as unknown response to prior therapy.

Patients will be randomized in a 1:1 fashion to receive Rucaparib 600mg twice daily vs. placebo continuously on a 28-day cycle until disease progression or other indication for discontinuation. Patients will be evaluated for progression of disease by history and physical exam every cycle as well as radiologically by CT imaging of chest/abdomen/pelvic every three cycles. Patients will be followed per study protocol from C1D1 for secondary outcomes.

Randomization will be stratified according the following criteria to ensure equivalent patient populations in Arms A & B; 1) Tumor histology of endometrioid, serous and other, 2) Number of previous lines of therapy, 1 or 2.

The study is designed as a 2-arm prospective superiority randomized clinical trial (RCT) with the following 2 treatment arms:

Arm A: Rucaparib 600 mg BID for 28 days

Arm B: Placebo 600 mg BID for 28 days

Study subjects will be randomized to the treatment arms in a 1:1 ratio. Patients and investigators, will be blinded to the randomization arms. Randomization schemas will be provided by study statisticians at the University of Colorado not involved in the randomization and collection of study data.

Treatment Duration: Chemotherapy cycles every 4 weeks (+/- 3 days) until progression of disease

Study duration including follow-up: 24 months following progression of disease

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

- Progression free survival (PFS)
  The primary endpoint of this study is progression free survival (PFS).
  Progression free survival is defined as cycle 1 day 1 (C1D1) till the time of progression as determined by RECIST 1.1 criteria or death.

4.2.2 SECONDARY ENDPOINTS

- Overall Survival
  Overall survival (OS) will be measured through routine follow-up.

- Overall survival is defined as cycle 1 day 1 (C1D1) till the time of death.

- Toxicity
  Toxicity will be assessed at cycle day 1 of each study cycle and day 28 following completion of therapy. Evaluation will include incidence and severity of adverse events and significant laboratory abnormalities. For laboratory parameters (CBC and CMP), changes of laboratory values over time (e.g., change from baseline summary statistics), grade shifts in laboratory values from baseline to worst on-study value, and grade 3 or higher toxicities a dose modification will be considered. If worsening of the condition persist after sufficient dose modification, the subject will be evaluated at start of next treatment cycles and may be removed from the study per provider's discretion.

1.2.3 EXPLORATORY ENDPOINTS

- Disease response in relation to molecular measures of BRCA and HRD status as well as mutational status of PTEN, PIK3CA, and AKT.
  The association between disease response (measured in a binary manner as "responded" or "did not respond") and several molecular measures (BRCA, HRD, PTEN, PIK3CA, AKT) will be explored. Archival tissue from the initial occurrence of disease and/or plasma collected on enrollment will be used to abstract these tumor markers.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a female aged 18-89.
4. Patients with a primary Stage III/IV or recurrent endometrial cancer
5. Patients have received at least one prior chemotherapy regimen and no more than two prior cytotoxic regimens (including hormonal therapy)
6. Primary chemotherapy regimen must have consisted of at least 4 completed cycles and no more than 8 completed cycles
7. Previous cytotoxic or radiation regimen at least 4 weeks before initiation and no more than 8 weeks from initiation after last dose of previous therapy

8. Patients who receive radiation to the whole pelvis or at least 50% of the spine must complete radiation therapy and have at least 4 weeks' time elapse prior to initiation of drug
9. ECOG performance status of 0, 1 or 2
10. ANC ≥ 1500 cells/μL
11. Platelet count > 100,000 μL
12. Hemoglobin ≥ 9.0 g/dL
13. Serum albumin ≥ 2.5 g/dL
14. Total bilirubin ≤ 1.5 x ULN
15. AST and ALT ≤ 3.0 x ULN
16. Serum Creatinine ≤ 1.5x ULN

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Inability to comply with study and follow-up procedures
2. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the past 3 months, unstable arrhythmias, or unstable angina
3. Known clinically significant liver disease defined as AST and ALT > 3.0 x ULN and/or Total bilirubin ≥ 1.5 x ULN, or documented history of active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease
4. Participation in investigational clinical trial within last 30 days
5. History of significant chronic disease including HIV/AIDS or hepatitis C
6. Inability to provide informed consent
7. Known CNS malignancy or CNS metastases
8. Patients with previous malignancy, other than endometrial, within the past 2 years from cycle 1, day 1, with the exception of those with negligible risk of mestastasis or death, such as adequately controlled basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the breast.
9. History of stroke or transient ischemic attack (TIA) within 3 months prior to cycle 1 day 1(C1D1)
10. Women with prognosis for survival less than 6 months
11. Patients who have progressed or have stable disease (SD) through most recent chemotherapy regimen
12. Patients deemed otherwise clinically unfit for clinical trial per Investigator's discretion
13. Patients with duodenal stent or other GI disorder/defect that would interfere with absorption of oral medication

14. Female patients who maintain fertility potential and refuse to comply to use contraception and be followed for pregnancy by pregncany testing
15. Minor surgical procedure <=14 days or major surgeries <=28 days prior to first dose of treatment

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential subjects will be identified and recruited from the investigators' clinical practice in gynecologic oncology. Potential subjects will present to clinic after completing chemotherapy for endometrial cancer and will not have shown progression at the time of enrollment.

Subjects who enroll in study will do so in accordance with their standard of care surveillance for their disease. This includes a surveillance visit and CT exam to assess recurrence every 3 months. Patients who are on therapy for their disease will be seen more frequently (at the start of each new cycle of therapy), per standard of care. Participants who conclude treatment early will be followed by phone and/or medical records at the completion of study.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request.

Reasons other than progression for study discontinuation can be due to patient desire, adverse events, or for any reason deemed appropriate by the investigator and/or sponsor.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participant will be discontinued from study if exhibiting continuing/worsening adverse or toxic events not improved with dose modification of the study therapy or for any other contraindication to the assigned treatment. End of treatment visit will be conducted at time participant is discontinued from the study. Reason for discontinuation should be documented on the early discontinuation CRF.

For participants discontinued from the study early, they will resume normal medical care. Treatment of any persisting adverse event will be per standard of care. If participant stops taking their medication prior to being discontinued or ending treatment by the investigator, they may be discontinued from the study and asked to return to the clinic for an end of treatment assessment.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) being developed for the treatment of cancer associated with homologous recombination deficiency (HRD). Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in cells, animal models and patients with a breast cancer gene 1 or 2 (BRCA1 and BRCA2) mutations in both clinical and nonclinical studies. Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with advanced ovarian cancer and metastatic castration-resistant prostate cancer (mCRPC) associated with HRD, including patients with a deleterious mutation in BRCA1, BRCA2 and other HR gene mutations.

6.1.1 ACQUISITION

Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338-BW and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied to the study sites by Clovis Oncology. The starting dose of rucaparib is 600 mg ingested BID. A brief description of the investigational product is provided below.

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation: (strengths expressed as free base)	Tablet; film coated; 200 mg (blue, round, debossed with C2), 250 mg (white, rounded diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3)
How Supplied:	200, 250, and 300 mg (as free base) strength tablets in 60 count HDPE bottles with child-resistant caps. Patients may receive one or more strengths.
Storage Conditions:	15 to 30° C (59 to 86° F).

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Rucaparib

The oral formulation of rucaparib contains the camphorsulfonic acid salt of the active agent rucaparib. All dosage strengths are expressed as the weight of free base rucaparib. Three strengths of oral rucaparib, 200 mg, 250 mg, and 300 mg are available as immediate-release film coated tablets. The 200 mg, 250 mg, and 300 mg tablets all contain the same ratios of active agent and excipients, with different strengths achieved by increasing the tablet weight.

The physical appearances of the tablets are unique in order to ensure proper identification. The 200 mg tablets are blue, round (11 mm) tablets de-bossed with 'C2'. The cosmetic blue film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, FD&C Blue #1 colorant, brilliant blue FCF aluminum lake, and FD&C blue indigo carmine aluminum lake. The 250 mg tablets are white, diamond shaped (15 mm x 11 mm) tablets de-bossed with 'C25'. The cosmetic white film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, and talc. The 300 mg tablets are yellow, oval tablets (16 mm x 8 mm) de-bossed with 'C3'. The cosmetic yellow film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and irradiated yellow iron oxide.

Placebo Tablet

Placebo tablets to match active tablets are available in all doses (200 mg, 250 mg, and 300 mg). These are identical in appearance and weight to the active tablets and contain the same excipients, but no active agent. Packaging and storage conditions are identical to the active tablets. Placebo tablets for oral administration will be supplied to the study sites by Clovis Oncology.

6.1.3 PRODUCT STORAGE AND STABILITY

All tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers between 15º and 30ºC (59 to 86° F).

6.1.4 PREPARATION

Rucaparib (formerly known as AG-014447 and PF-01367338) refers to the free base. The camphorsulfonic acid salt form (also referred to as camsylate) CO-338 (formerly known as PF-01367338-BW) is used in the clinical studies. CO-338 is formulated into a tablet for oral dosing. PF-01367338-09, a lyophilized powder for IV injection, and a glucuronate salt, PF-01367338-AU, were also developed and used in previous studies, but are no longer in development.

Camphorsulfonic acid salt form of rucaparib (CO-338, formerly known as PF-01367338-BW)
Laboratory Code: CO-338 (formerly known as PF-01367338-BW)
Molecular Weight: 555.67 Daltons (Da.)
IUPAC Name: 8-Fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt
Molecular Formula: $C_{19}H_{18}FN_3O$-$C_{10}H_{16}O_4S$
Physical Description: White to pale yellow powder

6.1.5 DOSING AND ADMINISTRATION

Rucaparib should be taken orally at 600 mg BID. Rucaparib tablets, or the equivalent of placebo, will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Medication will be provided in a blinded medication bottle dispensed from the investigational pharmacy. Patients will ingest the assigned treatment pill twice daily at about the same time every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz. (240 mL) of room temperature water with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described below.

6.1.6 ROUTE OF ADMINISTRATION

Oral

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

The recommended starting dose of rucaparib as continuously administered oral monotherapy is 600 mg BID. This dose will not be increased for the purpose of this study.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Dose reductions will be permitted for any SAE as listed in section 8, or any grade 3 AE at the discretion of the investigator. Reduction will be based on the following algorithm. Supportive care will be at the discretion of the investigator. The use of GCSF will be permitted.

Dose Reduction	Dose
Starting Dose	600 mg twice daily (two 300 mg tablets)
First Dose Reduction	500 mg twice daily (two 250 mg tablets)
Second Dose Reduction	400 mg twice daily (two 200 mg tablets)
Third Dose Reduction*	300 mg twice daily (one 300 mg tablet)

* Consult with investigator-sponsor before reducing to dose level 3. Further dose reduction may be possible, but require consultation with the investigator-sponsor.

Treatment Hold Criteria

Treatment with rucaparib should be held if any of the following are observed and a dose reduction should be considered or implemented.

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below.

- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Rucaparib Re-Treatment Criteria

Treatment may resume if:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below.

6.1.9 MANAGEMENT OF RUCAPARIB TREATMENT-EMERGENT SAES REQUIRING DOSE REDUCTIONS

Management of Anemia including evaluation for MDS/AML and follow-up of patients who discontinue treatment with ongoing anemia:

- If the patient develops anemia CTCAE Grade ≥ 3, treatment should be held until the anemia improves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.
- If the duration of dosing is interrupted for > 14 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed between the investigator and the sponsor.
- In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event.
- If the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
- The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

Management of ALT/AST Elevations:

Grade 3 ALT/AST elevations have been successfully treated with treatment interruption and/or a reduction in dose. The data reported as of the data cut-off date suggest that many patients have been able to continue treatment with 600 mg BID following a dose interruption, without any further elevation or recurrence of Grade 3 ALT/AST. The following guidelines have been suggested for managing Grade 3/4 ALT/AST elevations.

* Grade 4 ALT/AST elevations: hold treatment until values have returned to Grade 2 or better, then resume treatment with a dose reduction. Monitor liver function tests weekly for 3 weeks after treatment has been restarted.

* Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
    - Monitor liver function tests weekly until resolution to ≤ Grade 2.
    - Continuation of treatment with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.
    - If patient has Grade 3 ALT/AST and continues on treatment, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before treatment can be resumed, either at the current dose or at a reduced dose.

Management of Myelosuppression:

Grade 3/4 myelosuppressive events have been successfully treated with supportive care and dose interruption/reduction. Additional diagnostic evaluation, including bone marrow examination, should be considered for patients with persistent myelosuppression that does not stabilize or recover with treatment modification.
Dose re-escalation upon improvement of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the investigator.

6.1.10 DURATION OF THERAPY

Duration of study therapy will be until progression of disease as determined by treating provider in agreement with local study PI. In the event that treating provider and local PI do not agree, national study PI will determine progression status.

6.1.11 TRACKING OF DOSE

Dose modifications will be tracked on the case research form (CRF) at time of event.
Medication adherence will be calculated by return of unused medication at the completion of each treatment cycle.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The institutional pharmacy is responsible for managing the inventory of rucaparib for the IIT. Rucaparib supply shipments from Clovis, or its designee to the pharmacy will be made on an agreed upon schedule based on enrollment in the IIT.

6.2.1 RECEIPT OF STUDY DRUG

Clovis oncology will provide study sites with blinded drug kits to be supplied to the patient via the site investigation drug pharmacy. Rucaparib supplies will be shipped to the address and attention of: Principal Investigator or designee, and the institution pharmacist or designee. If this address or contact person should change, please inform Clovis so that the records can be updated and shipments are redirected to the appropriate location/study personnel.

Please follow the instructions below when receiving study drug at your site:
Step 1: Upon receipt, the rucaparib investigational product shipping box should be immediately opened, and the STEMS monitor located and reviewed.
Step 2: Upload the STEMS monitor information at *www.almacstems.com*.
Step 3: Upon upload of the STEMS monitor information, print the temperature report and file with the rucaparib investigational product documents.
Step 4: If the STEMS monitor is not displaying an alarm, the rucaparib investigational product supplies are ready to be used. Please store the supplies in a temperature-controlled, locked, limited-access area. Proceed to Step 6.
Step 5: If the STEMS monitor displays an alarm, please:

- Quarantine the rucaparib supplies in a temperature-controlled, locked, limited-access area until further notice from Clovis.
- Send an email to ***Rucasupply@clovisoncology.com*** indicating that a rucaparib shipment has been received and the temperature monitor is displaying an alarm.
- A Clovis Oncology clinical supply team member will be in touch with further instructions

Step 6: After the STEMS monitor has been registered with Almac and the temperature report printed, the monitor may be destroyed.

- Please note that the STEMS monitor has a lithium battery in it, so it should be disposed of in a manner compliant with local regulations.

6.2.2 REPORTING OF DAMAGED, MISSING, OR LOST STUDY DRUG

Please follow the instruction below when study drug is noted as damaged or missing at the site or with patient. This process also applies if study drug was lost or misplaced by a patient.

Damaged or Missing upon receipt of a shipment If study drug tablets or study drug bottles are observed to be damaged or missing upon receipt, please notify your MSL and Clovis Supply Chain (*RucaSupply@ClovisOncology.com*) within 48 hours by completing and submitting the provided **Investigational Product Incident Report Form** to trigger an investigation, if required.

Please contact Clovis Supply Chain and your MSL prior to destroying any damaged, expired or end of study drug. The pharmacist or designee must complete and submit the **Study Drug Destruction Authorization Form** to Clovis for those three cases only to obtain approval from Clovis before destruction. Standard returns and empty bottles may be destroyed per site SOPs,

after all site drug accountability is completed. All drug destruction certifications and documentations should be stored in study files at the site.

If the study drug must be destroyed, please follow the instructions listed in the Destruction of Study Drug.

Damaged during site storage If study drug tablets or study drug bottles are noted as damaged while being stored at the site, please complete the **Investigational Product Incident Report Form** and send to your MSL and Clovis Supply Chain (*RucaSupply@ClovisOncology.com*) within 48 hrs. of knowledge of the issue to obtain further instructions.

Clovis Supply Chain will conduct an investigation and determine whether the bottle(s) is still usable or should be destroyed.

If the study drug must be destroyed, please follow the instructions listed in the Destruction of Study Drug.

Missing during site storage If study drug goes missing during site storage, please complete the **Investigational Product Incident Report Form** and send to your MSL and Clovis Supply chain (*RucaSupply@ClovisOncology.com*) within 48 hrs. of knowledge of the issue to obtain further instructions.

Bottles or tablets are damaged during patient use If the study drug tablet(s) is damaged or the bottle tamper seal is damaged or missing after being provided to the patient, you must collect the damaged bottle(s) from the patient and complete an **Investigational Product Incident Report Form**.

If the study drug must be destroyed, please follow the instructions listed in the Destruction of Study Drug and follow your local requirements.

Bottles missing during patient use If a bottle or bottles of study drug go missing after being provided to the patient, additional bottle(s) should be dispensed from the current drug supply, and documented on the drug accountability record. If needed, please contact Clovis Supply Chain by email (RucaSupply@clovisoncology.com).

Individual tablets damaged or missing during patient use If individual tablets are damaged or go missing during patient use, an additional bottle should be dispensed from the current drug supply, and documented on the drug accountability record. If needed, please contact Clovis Supply Chain by email (*RucaSupply@clovisoncology.com)*.

6.2.3 DISPENSATION OF STUDY DRUG

Please follow the instructions below when dispensing study drug at your site:

- Determine quantity of bottles and strength to dispense to each patient.

- Complete the provided **IIT Investigational Product Patient Dispensing Log** or equivalent log.

6.2.4 TEMPERATURE EXCURSIONS OF STUDY DRUG

Please follow the instructions below when an excursion occurs while study drug is stored at your institution:

- Clovis permits allowable excursions; refer to Clovis Allowable Excursion memo for 01Dec2015 for details. Should the excursion fall within the allowable range, site may proceed to use product after documenting excursion in site logs and records. There is no need to contact Clovis unless the excursion falls outside the instance and cumulative range on the memo.
- If the excursion is outside allowable range, segregate affected supply in a location separate from any unaffected study drug. Clearly mark study drug in question as "Quarantined" to ensure it is not used while excursion is being evaluated and follow the remaining 3 bullets below.
- Notify Clovis Supply Chain as soon as possible after the excursion is. All storage temperature excursions affecting study drug, regardless of whether Clovis authorization for continued use is allowed, should be clearly documented in temperature logs or other appropriate documents maintained at the site.
- Complete the provided **Investigational Product Incident Report Form** and send to Clovis Supply Chain (*RucaSupply@ClovisOncology.com*) and to your MSL via email within 24-48 hours of excursion being identified, along with complete temperature logs or recordings for duration of excursion. If all study drug is affected and site has ongoing patients, submit form to Clovis immediately.
- Following an assessment by Clovis Supply Chain, notification of the final disposition of the study drug will be sent to the site accordingly.

6.2.5 DESTRUCTION OF STUDY DRUG

It is expected that returned, unused by assigned patient, damaged, expired or otherwise out of specification study drug will be destroyed by the site, using internal site procedures for the safe disposal of cytotoxic materials.

6.2.6 SITE DRUG ACCOUNTABILITY AND RECONCILIATION

NOTE: Drug accountability is an Investigator GCP requirement for IITs. All participating institutions must retain copies of all study drug inventory records, packing lists, and other shipping documents (e.g. invoices and receipts upon delivery from the study drug depot), prescriptions for dispensing, delivery cartons, etc. for accountability of the drug. Accountability should be ongoing per pharmacy and protocol requirements, as applicable.

Physical product inventories should be routinely reconciled against study accountability logs. If any discrepancies are identified, pharmacy personnel must attempt to reconcile all such discrepancies. The discrepancies should be clearly explained in the accountability logs or other appropriate documentation, and the process of reconciliation and resolution must be clearly documented.

The provided **IIT Investigational Product Temperature Log, IIT Investigational Product Patient Dispensing Log**, and **IIT Investigational Inventory Log** are tools which can be used to document accountability. Site-created logs/accountability documents may be used instead of the Clovis-supplied logs.

The pharmacist or other appropriate site personnel should document in the site's pharmacy accountability record/log each time study drug is:

- Received from the drug depot
- Dispensed to a study patient
- Subjected to a temperature excursion
- Returned / Quarantined / Missing / Damaged / Destroyed

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATION

Treatment will include Rucaparib 600mg PO BID in arm A vs placebo pills PO BID in arm B to be taken on a daily basis on a 28-day cycle until disease progression or other indication for study discontinuation. Reasons other than progression for study discontinuation can be due to patient desire, adverse events, or for any reason deemed appropriate by the investigator and/or sponsor. Discontinuation of therapy for greater than 28 days due to AE's will also result in discontinuation of study. Initiation of treatment must occur between 4 and 8 weeks of last dosing of prior therapy.

The treatment period is cycles of 28 days until progression of disease. Patients will be evaluated at the beginning of every cycle and will undergo CT imaging of the chest, abdomen and pelvis at the completion of every 3 cycles (+/- 7 days) for evaluation of progression of disease and adverse events. Progression will be classified based on RECIST 1.1 criteria. If a patient has been on study 24 months, patient evaluations may be decreased to every 3 cycles at the providers discretion.

7.1.1 CLINICAL ASSESSMENTS

ECOG performance status

ECOG Score	Criterion
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

RECIST 1.1 guidelines for tumor response [21]

Evaluation of Target lesions	
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesion, taking as reference the baseline sum LD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR not sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Progressive Disease (PD)	At least a 20% increase in the sum of LD of target lesions, taking in reference the smallest sum LD recorded since the treatment started or the appearance of one of more new lesions
Evaluation of Non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker levels
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS (RESEARCH PROCEDURES)

Samples for hematology, serum chemistry, and serum pregnancy will be analyzed by a local laboratory. The panels of laboratory tests to be performed are shown below:

Hematology (CBC): red blood cells (RBC) and parameters (hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]), white blood cells (WBC) and differential (with ANC), and platelet count will be assessed at screening, during treatment at each study visit, and at the

treatment discontinuation visit for all patients. Hematology results must be reviewed by the investigator before the start of treatment with study drug and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.

Serum Chemistry (CMP): total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, glucose, sodium, potassium, chloride, CO2, and calcium), at screening, during treatment at each study visit, and at the treatment discontinuation visit for all patients. Fasting is not required before blood sampling. Serum chemistry results must be reviewed by the investigator before the start of treatment with study drug and ongoing at times testing occurs.

Lipid Profile: total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) at baseline (C1D1) and at the treatment discontinuation visit for all patients. Fasting is not required before blood sampling.

Serum Pregnancy: for women of childbearing potential only. A serum pregnancy test must be performed ≤ 3 days prior to first dose of study drug (a negative result is required before dosing can begin) and at the treatment discontinuation visit (unless the woman has undergone surgical menopause by hysterectomy). A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase, and a serum pregnancy test performed at Treatment Discontinuation. A positive serum pregnancy test during study participation must be reported to the Sponsor. Refer to section below (Pregnancy or Drug Exposure during Pregnancy) for details.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE. Refer to Section 10.5 for guidelines on reporting of abnormal laboratory values as AEs.

7.2.2 OTHER ASSAYS OR PROCEDURES (RESEARCH)

Tumor genetic screening of DNA extracted from microdissected tumor tissue will be used to test for mutations in the study genes of interest: HRD, BRCA, PTEN, PIK3CA and AKT. [22]
Tumor will be collected from surgical pathology specimans using archival tissue (initial tumor specimen) or recent current disease biopsy (when available). Plasma will be collected on C1D1.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Collection of blood at the baseline visit (C1D1) will be used as source for germline DNA. Collection may be used for further future DNA analysis. Collection kits provided by the University of Colorado Biorepository Core Facility will be used for the blood collection. Blood collected at University of Colorado will be processed by the Biorepository. Blood from external sites will be

processed locally and shipped to the Biorepository, provided collection kits include all the components to process, aliquot, and store blood specimens. Archival formalin-fixed paraffin-embedded (FFPE) tissue from diagnostic and/or surgical procedures will be used for the extraction of tumor DNA for future mutation analysis. Archival FFPE specimens will be requested from the participating sites and where needed the participating sites will retrieve the materials from secondary sites where procedures where performed. Preferably a representative tissue block will be submitted but in cases where release of a block is prohibited submission of 15 unstained tissue sections will be accepted. After the archival FFPE specimens are received by the Biorepository specimens data will be logged in the database and transferred to the Colorado Molecular Pathology Shared Resource (CMCO) laboratory for sectioning, pathological evaluation, macrodissection (if needed), and DNA extraction. Where possible 15 blanks section will be prepared for banking and future research studies. After DNA extraction the FFPE blocks will be transferred to the biorepository to be returned to the originating site. Representative H&E slides of the specimens will provided to the Biorepository for digital imaging to create a permanent research record. Data on processing and DNA metrics will be recorded in the database. Specimens will be stored for future use.

7.2.4 SPECIMEN SHIPMENT

Archival specimen shipping kits will be provided to the external sites for transfer of the FFPE materials. The specimen shipping kits will contain all the materials needed to pack and ship the blocks and/or slides to the biorepository. The Biorepository will ship FFPE blocks back to the external participating sites after DNA isolation is completed. Blood specimens will be processed locally by the external sites and stored at -80^{o}C until shipment. The biorepository will provide a shipping kit that, besides dry ice, will include all the components to pack and ship blood specimens in batches to the biorepository. Dry ice shipments will occur Monday to Wednesday only to allow for timely delivery before the weekend.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

The screening visit will be conducted 0-28 days prior to Cycle 1 Day 1 (C1D1). This visit will include the following procedures/assessments:

- Informed Consent;
- Confirm Eligibility;
- Physical examination;
- Height/Weight;
- Vitals (temperature, pulse, blood pressure, respiratory rate);
- Medical History;

- Baseline adverse events;
- Concomitant medications and procedures;
- Disease/tumor assessment;
- ECOG performance status;
- Hematology;
- Serum chemistry (fasting is not required);
- 12-lead ECG;
  CT imaging chest/abdomen/pelvis (completed 0-28 days prior to C1D1; does not have to be same day as screening).

7.3.2 ENROLLMENT/BASELINE

Cycle 1 Day 1

The enrollment/baseline visit will be conducted C1D1. This visit will include the following procedures/assessments:

- Confirm eligibility;
- Hematology;
- Lipid profile;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential/not underwent surgical menopause; (≤ 3 days prior to start of every cycle);
- Physical examination;
- Weight;
- Vitals (temperature, pulse, blood pressure, respiratory rate);
- Baseline adverse events;
- Concomitant medications and procedures;
- Genetic molecular testing (obtained by archival tissue and/or serum/plasma analysis).
- Randomization of study medication;
- Administration of study medication.

7.3.3 TREATMENT

Cycle 2 +, Day 1

Study treatment will be conducted until disease progression or other reason for discontinuation. Cycles will be 28 days long of therapy with window of +/- 3 days for evaluation. Study treatment follow-up will include the following procedures/assessments:

- Study medication adherence and modification (as needed);
- Administration of study medication;
- Physical examination;
- Weight;
- Vitals (temperature, pulse, blood pressure, respiratory rate);
- Concomitant medications and procedures;

- AE assessment;
- Hematology;
- Serum chemistry (fasting is not required);
- Disease/ tumor assessment;
- Serum pregnancy for women of childbearing potential/not underwent surgical menopause; (≤ 3 days prior to start of every cycle);
- CT imaging chest/abdomen/pelvis (to be conducted at completion of every 3rd cycle +/- 7 days).

7.3.4 FINAL STUDY TREATMENT VISIT

End of treatment will be conducted 28 days (+14 days) following completion of treatment. End of treatment will include the following procedures/assessments:

- Discontinuation of study medication;
- Physical examination;
- Weight;
- Vitals (temperature, pulse, blood pressure, respiratory rate);
- Concomitant medications and procedures;
- AE assessment;
- Hematology;
- Lipid profile;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential/not underwent surgical menopause.
- Disease/ tumor assessment;
- CT imaging chest/abdomen/pelvis (to be conducted at completion of study +/- 28 days from discontinuation of study medication).

7.3.5 FOLLOW-UP

For all subjects, annual follow-up visit (+/- 30 days) will be conducted via phone or medical records from the time of enrollment (C1D1) and will include the following assessment:

- Survival

7.3.6 EARLY TERMINATION

Subjects who meet the primary endpoint (progression/recurrence/death) or severe toxicity requiring removal from study, an end of treatment visit will be conducted as appropriate.

7.3.7 UNSCHEDULED VISIT

Unscheduled visits may be conducted in the event of an SAE/AE or toxic event. ***The following assessments/procedures should be considered if appropriate*:**

- Study medication adherence and modification;
- Discontinuation of study medication;
- Physical examination;
- Weight;
- Vitals (temperature, pulse, blood pressure, respiratory rate);
- Concomitant medications and procedures;
- AE assessment;
- Hematology;
- Serum chemistry (fasting is not required);
- Serum pregnancy for women of childbearing potential/not underwent surgical menopause;
- CT scan chest/abdomen/pelvis;
- Disease/ tumor assessment.

For subjects requiring permanent termination of the study drug, subject should be discontinued from the study.

7.3.8 SCHEDULE OF EVENTS TABLE

SCHEDULE OF STUDY ASSESSMENTS

Study Visits	**Screening**	**C1D1**	**Cycles 2+ Day 1[9]**	**End of Treatment**	**Unscheduled Visit[7]**	**Annual Follow-Up**
	Day -28 to Day 0	*Baseline*	*28 Day cycle (+/- 3 days)*	*28 (+14) days*		*12 months (+/-30 days)*
Procedures						
Informed consent	X					
Confirm eligibility (Inclusion/exclusion criteria)	X	X				
Randomization		X				
Medical History	X					
Disease/Tumor assessment	X		X[6]	X[6]	X[6]	

Concomitant Medications and Procedures	X	X	X	X	X	
Baseline AE review	X	X				
Adverse Events			X	X	X	
Physical Exam[1]	X	X	X	X	X	
ECOG performance status	X					
Height/weight[2]	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	
CBC	X	X	X	X	X	
CMP	X	X	X	X	X	
Lipid Panel		X		X		
Serum pregnancy[4]		X	X	X	X	
ECG	X					
Genetic molecular tissue/plasma collection		X				
Study treatment provided		X	X			
Medication adherence and modification			X	X	X	
Discontinuation of medication				X	X	
CT imaging chest/abdomen/pelvis	X		X[6]	X	X	
Survival status[5]						X[8]

[1] Physical exam should include at minimum cardiac, lung and abdominal exam.
[2] Height only needs to be measured at enrollment visit.
[3]Temperature, pulse, blood pressure, respiratory rate.
[4] For women of childbearing potential/not underwent surgical menopause; (≤ 3 days prior to start of every cycle);
[5] Conducted by phone or medical record
[6] CT scan performed prior to enrollment, at conclusion of every 3rd cycle +/- 7 days, and at time of suspected recurrence (unanticipated visit) as appropriate; review of CT RECIST criteria will be conducted at screening, following completion of every 3rd cycle and at end of treatment.
[7] Unscheduled visit assessments/procedures should be considered if appropriate
[8] Annual follow-up from time of end of study treatment via phone call assessment of survival and AE's until notification of patient death
[9] If patient has completed 24 cycles, evaluations can be completed every 3 cycles at providers discretion

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication

that can be prescribed only by a properly authorized/licensed clinician. Medications reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.4.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Effect of Other Medicinal Products or Concomitant Drugs on Rucaparib

Enzymes responsible for rucaparib metabolism have not been identified. Based on in vitro data, CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. In population PK analysis, patients with different CYP2D6 or CYP1A2 genotypes showed comparable rucaparib PK. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

Effects of Rucaparib on Other Medicinal Products or Concomitant Drugs

At the steady-state following treatment with 600 mg rucaparib BID, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibits P-gp in the gut, but this is unlikely to be clinically significant.

CYP1A2 Substrates

When co-administering medicinal products metabolized by CYP1A2, particularly medicines which have a narrow therapeutic index (eg, tizanidine, theophylline), dose adjustments may be considered based on appropriate clinical monitoring.

CYP2C9 Substrates

When co-administering medicinal products that are CYP2C9 substrates with a narrow therapeutic index (eg, warfarin, phenytoin), dose adjustments may be considered, if clinically indicated. Exercise caution and consider additional International Normalised Ratio (INR) monitoring with co-administration of warfarin and therapeutic drug level monitoring of phenytoin, if used concomitantly with rucaparib.

CYP2C19 Substrates

No dose adjustment is considered necessary for co-administered medicinal products that are CYP2C19 substrates.

CYP3A Substrates

Caution is advised when co-administering medicinal products that are CYP3A substrates with a narrow therapeutic index (eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine,

ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine). Dose adjustments may be considered, if clinically indicated based on observed AEs.

P-gp Substrates

No dose adjustment is recommended for co-administered medicinal products that are P-gp substrates.

Other Enzymes and Transporters

Interaction of rucaparib with other enzymes and transporters was evaluated in vitro. Rucaparib is a weak inhibitor of CYP2C8, CYP2D6, and UGT1A1. Rucaparib down regulated CYP2B6 in human hepatocytes at clinically relevant exposures. In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with an IC50 value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrates (eg, rosuvastatin).

Effect of Food on Rucaparib Exposures

A high-fat meal increased Cmax by 20% and increased AUC0-24 by 38%. The effect is not considered clinically significant. In clinical studies, rucaparib was administered with or without food.

Effect of Proton Pump Inhibitors on Rucaparib Exposures

In a population PK analysis, concomitant administration of a PPI had no clinically meaningful impact on rucaparib PK.

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

There are no prohibited concomitant medications for this trial.

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Subjects will be allowed to take GCSF therapies while on study.

7.7 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Study drug will not be provided to the patient after their end of study participation

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (e.g., “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify as an AE (and hence documented on the AE eCRF, not on the physical examination eCRF, which is reserved for physical signs or findings).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is any untoward medical occurrence that occurs at any dose (or, occurs after informed consent is given and prior to dosing if the SAE is related to a study procedure) that:

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity

- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (e.g., respite care)
- Hospital visits of less than 24 hours' duration (e.g., patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an SAE with CTCAE Grade 5 (fatal outcome) indicated.

Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant.

8.1.3 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

Clovis Oncology is interested in the following adverse events of special interest (AESI): myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Section 6.1.9 describes

the appropriate follow-up and discontinuation of therapy for patients experiencing either of these AESIs.

As of 27 June 2016, there have been three events of myelodysplastic syndrome (MDS) and three events of acute myeloid leukemia (AML) reported in patients participating in Clovis-sponsored clinical studies. The three events of MDS were reported in open-label studies CO-338-017 (ARIEL2) (n = 2) and CO-338-010 (n = 1). One event of AML was reported in the open-label study CO-338-017, and two events of AML (one was fatal) were reported in blinded, randomized study CO-338-014 (ARIEL3).

More than 1,000 patients have received oral rucaparib in Clovis-sponsored studies as 27 June 2016, thus these events have been observed in < 0.6% of all patients treated in these studies. Events of MDS and AML have also been reported with another PARPi [23]. All patients experiencing these events received prior treatment with chemotherapy. While the etiology of these events is confounded by prior treatments and the relationship to rucaparib is not clear, Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). Adverse events of special interest (AESIs) (both serious and non-serious) will be reported to Clovis within 48 business hours of awareness and will continue to be reported to Clovis.

8.1.4 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during study participation (beginning at the time informed consent is obtained) and until 28 days after the last dose of study drug. After the 28-day window, only treatment-related SAEs and all AESIs, irrespective of causality, need to be reported. In the time after informed consent is provided but before study drug is administered, AEs/ SAEs are to be recorded if they are the result of a study-related procedure. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03) and recorded on the eCRF.

8.2.1 SEVERITY OF EVENT

The severity of each AE will be graded using the NCI CTCAE, Version 4.03 grading scale [24].

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Life-threatening** – Life-threatening events require urgent intervention to prevent death
- **Fatal** – Death

8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to the study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

Not Related To Study Drug	• An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of the study drug. • It does not follow a known pattern of response to study drug • It does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.
Related to Study Drug	• An AE that is difficult to assign to alternative causes. • It follows a strong or reasonable temporal sequence from administration of study drug. • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • It follows a known response pattern to study drug • It is confirmed with a positive rechallenge or supporting laboratory data.

Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug (note all that apply)

- None
- Dose reduced/delayed
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving
- Ongoing
- Death
- Lost to follow-up

8.2.3 EXPECTED ADVERSE EVENTS

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the reference safety information of the investigator brochure previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 28 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose of study drug. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, or until lost to follow-up. After the 28-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF. Any AE that occurs after first dose of study drug through 28 days after receiving the last dose of study drug will be recorded on the AE eCRF.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

SAEs and AESIs that occur during the study or within 28 days after receiving the last dose of study drug, whether or not related to study drug, must be reported to Clovis immediately (i.e., within 48 hours or 2 calendar days from knowledge of the event) to the Sponsor/ SAE designee. Secondary sites will report SAEs and AESIs to the coordinating site for report to the sponsor. The contact information for reporting of SAEs/ AESIs can be found on the SAE/ AESI Reporting Form. After the 28-day reporting window after discontinuation of randomized treatment only SAEs assessed as related to study drug and all AESIs, irrespective of causality, need to be reported. Information on the follow-up of AEs, SAEs, and AESIs is provided below.

Clovis or the Sponsor-Investigator's study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See **Study Contact Listing** for contact information.
- Other SAEs, regardless of relationship, will be submitted to the study sponsor within 5 days of site awareness.

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report form. It is the site PI's responsibility to report UAPs to their IRB, using the IRB's standard UAP form. The Lead PI is responsible for reporting the UAP to the UCCC DSMC, if applicable. If an IRB UAP form is not provided, the UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UAPs that are SAEs will be reported to the IRB and study sponsor within five (5) days of the investigator becoming aware of the event.
- Any other UAP will be reported to the IRB and study sponsor at annual review.

8.4.4 REPORTING OF PREGNANCY

Based on the finding that rucaparib was embryotoxic at all doses administered in the embryofetal development study and the potential of PARP inhibitors to affect spermatogenesis (See IB, Section 6.2.2), it is advised that patients of reproductive potential and their opposite sex partners of reproductive potential practice a highly effective method of contraception during and after treatment with rucaparib as specified per protocol. Specifically, female patients of childbearing potential and their male partners are advised to practice a highly effective method of contraception during treatment with rucaparib and for 6 months following the last dose of rucaparib.

A woman is considered to be of childbearing potential unless one of the following applies:

- Is considered to be permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- Is postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

Highly effective contraception is considered to be a method with a < 1% per year failure rate. Recommendations for highly effective contraception while taking rucaparib include:

- Ongoing use of injectable or implantable progesterone
- Placement of an intrauterine device or intrauterine system
- Bilateral tubal occlusion
- Complete (as opposed to periodic) abstinence
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate

In addition, monthly serum pregnancy testing is recommended for women of childbearing potential taking rucaparib. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib.

Pregnancies should be reported to the sponsor using the pregnancy report form

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient during study participation or within 6 months of last dosing must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE.

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the Sponsor.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/AESI processes using the appropriate AE or SAE/AESI forms.

8.5 SAFETY OVERSIGHT

Medical Monitoring

Medical monitoring and monitoring of SAEs across all sites will be monitored by Dr. Bradley Corr on a continuous basis. All SAEs must be reported to Dr. Corr at the University of Colorado within

48 hours of event. The sponsoring site will be responsible for reporting such events to the overseeing IRB and the sponsor within 5 days of event.

Data Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The PI will provide a DSM report to the CU Cancer Center DSMC on a six-month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six-month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

The coordinating site (UCD) is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's six month DSM report to the DSMC to include minutes from monthly PI teleconferences. The Clinical Trials Office at UCD will provide monitoring of

the coordinating site. The data manger will provide additional internal data validation for the coordinating site and monitoring for all additional participating sires. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six-month review to their IRB of record at the time of continuing review.

9 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Clinical monitoring of the study will be conducted by research personnel (data manager) from the University of Colorado Denver for all additional sites. The University of Colorado will conduct their own audit and validation of study entry with internal research personnel through the Clinical Trials office. In order to conduct monitoring, study sites should make staff and resources available for the following:

- Initial in-service of the study site, including investigator training and site tour
- Regular attendance of progress meetings
- Research staff available for interim monitoring visits
- All study documents (consents, CRFs, etc.…) available for site visits in which the monitor will verify accuracy of data as entered into the electronic database
- Response to data requests via fax/email if site visit is not necessitated
- Maintenance of all regulatory documents and accessible for monitor review (UCD may request these be sent to the lead site for regulatory maintenance)
- Research staff available to response to data queries and resolve inconsistencies in study records
- Close out of the study at the study site

The study monitor will provide each site with a report of the monitor visit to be submitted to their local IRB. In addition to monitoring visits, a monthly conference call will take place among all sites to discuss treatment outcomes, enrollment, significant toxicities, dose modifications and responses. These meetings will be documents and the minutes shared with all sites.

Additionally, the University of Colorado Cancer Center DSMC will conduct independent audits of study sites to evaluate conduct and compliance of the investigational protocol as a study site. All study documents and regulatory documents must be available to audit. The audit reviewer will also require direct access to study source (participant medical records relating to study) and time with the site investigator and/or regulatory personnel during their visit.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A modified intent-to-treat analysis will be based on participants initiating assigned medication for first day of treatment. All participants randomized who receive the assigned study medication at least once will be included for analysis.

Data will be abstracted regarding participant demographics, disease status, adverse/toxicity, and clinical endpoints (progression and survival). This is a comparative study designed to assess the efficacy with use of maintenance Rucaparib for women with recurrent and/or metastatic endometrial cancer compared to placebo. Secondary endpoints will assess the efficacy for overall survival, specific genetic markers, and toxicity.

Treatment will be taken for 28 consecutive day cycles until progression of disease or death with follow-up continuing for 24 months after discontinuation of study treatment. Progression free survival (in months) will be compared between the treatment arm A (Rucaparib 600mg BID) and arm B (placebo control). Biostatisticians will remain blinded to the treatment arm assignments during analysis.

Participants will be analyzed employing a modified intention-to-treat approach (analyzed based on receiving assigned study medication at least once). Participants will not be allowed to change treatment arms while on trial.

10.2 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  We hypothesize that the use of PARP inhibitor maintenance therapy will improve PFS by a median of 4 months compared to placebo in patients with recurrent or metastatic endometrial cancer who have completed standard first line chemotherapy.

- Secondary Efficacy Endpoint(s):
  We hypothesize that the use of PARP inhibitor maintenance therapy will improve OS compared to placebo in patients with recurrent or metastatic endometrial cancer who have completed standard first line chemotherapy.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Descriptive statistics using means, frequencies, and percentages will be computed to describe the study population. Participant data will be analyzed employing the intention-to-treat approach. Student's t-tests (for continuous variables) and chi-square tests (for categorical variables) will be used to compare the two groups for demographic and secondary outcome variables. A *p*-value of <0.05 will be used to demonstrate statistical significance for secondary outcomes. For the primary outcome measure, progression free survival, and the secondary outcome, overall survival, Kaplan-Meier curves will be displayed and the log-rank test will be used to compare the curves between the two arms. Cox regression model will be used to identify significant predictors associated with the primary outcome. The log-rank test and Cox model will be stratified based on the randomization strata. IBM SPSS version 24, SAS, or R will be used for all statistical analyses.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary objective of this study is to test efficacy in **progression free survival** (PFS) in Arm A when compared to Arm B. Progression free survival will be determined from start of study treatment till time of progression as detected by CT exam and determined by RECIST 1.1 criteria. Kaplan-Meier curves will be displayed and log-rank test will be used to compare the curves between the two arms. Cox proportional hazard model will be used to determine hazard ratio. A one sided hypothesis test with an alpha of 0.10 will be used to assess whether a significant difference exists between the treatment arms.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Overall survival (OS) will be compared between the treatment groups. OS will be tested using log-rank test in the same manner as for the primary endpoint. A one sided hypothesis test with an alpha of 0.10 will be used to assess whether a significant difference exists between the treatment arms.

10.4.4 SAFETY ANALYSES

Safety evaluation will include incidence and severity of adverse events and significant laboratory abnormalities. Safety analysis will be performed on all patients who received at least one dose of the treatment drug. Safety and tolerability will be tabulated by system organ class and preferred term. Tables of serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will also be provided. Summary statistic will be provided for total number of doses, average dose administered, and duration of treatment.

For select laboratory parameters, changes of laboratory values over time (e.g., change from baseline summary statistics), grade shifts in laboratory values from baseline to worst on-study value, and grade 3 or higher laboratory toxicities will be summarized.

Incidence of AEs and SAEs will be compared between treatment arms using chi-square analysis. A p-value of <0.05 will be used to demonstrate statistical significance.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Adherence and retention of study therapy be described by treatment delays and early terminations due to therapy toxicities.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics using means, frequencies, and percentages will be computed to describe the study population. Participant data will be analyzed employing the intention-to-treat approach. Student's t-tests (for continuous variables) and chi-square tests (for categorical variables) will be used to compare the two groups for demographic and secondary outcome variables.

10.4.7 EXPLORATORY ANALYSES

Disease response for molecular measures (BRCA, HRD, PTEN, PIK3CA, AKT)
To evaluate the association between disease response (measured in a binary manner as "responded" or "did not respond") and several molecular measures (BRCA, HRD, PTEN, PIK3CA, AKT). Associations of response with categorical measures will be tested using Pearson's chi-square test, each test controlling the type 1 error rate at 0.05.

10.5 SAMPLE SIZE

Using a median PFS of 8 months based on GOG 177 data and an expected improvement of 4 months median PFS to 12 months, we estimate we will need a sample size of 123 patients total to determine significance with a hazard ratio of 0.67. This sample size was estimated using a one-sided alpha of 0.1 and a power of 0.8. In addition, an accrual time of 23 months (explained below) and a total study period of 48 months was assumed. We will add an additional 12% of patients for withdrawals for a total sample size of 138 (69 per arm).

This study will be conducted over 48 months. This allows for ~23 months of accrual, followed by 24 months of follow-up to complete the study. The University of Colorado sees on average 5 cases of recurrent endometrial cancer/month. Assuming that half of the patients approached will meet eligibility and consent to participate, we can estimate 2.5 subjects enrolled per month at the coordinating site. We anticipate similar recruitment/enrollment goals from the secondary sites. The secondary sites will accrue for approximately 16 months with an additional 24 months of

follow-up. The lag of time accounts for the sub-contract and study site approval process at the secondary site. With UCD accruing for 23 months and the secondary sites accruing for 16 months each all at a rate of 2.5 subjects per month, we can meet our enrollment goals at 23 months. Again, all sites will have a 24-month follow-up time bring the total study duration to 4 years, or 48 months total.

10.6 MEASURES TO MINIMIZE BIAS

We will use the following methods to minimize bias for this trial:

- Participation bias: We will employ a double-blinding by participants and study investigators.
- Selection bias: Participants will be randomized 1:1 to treatment arms.
- Confounding: the following variables will be stratified between treatment arms to minimize any potential confounding: tumor histology. Additional variables will be considered for stratification in the analysis to determine if confounding exists (prior # of therapies, response to previous therapy).

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Participants will be randomized on C1D1 after confirmation of eligibility and consent. The Biostatistician at UCD will provide the randomization schema to each study site. Medication will be blinded by the drug sponsor, Clovis, prior to arriving to the clinical research site. Study sites will receive the blinded medication directly from the study sponsor and will be stored at the study sites' investigational pharmacy. Medication will be prescribed as either treatment A or treatment B and masked in two identical bottles. The participant will continue to receive the same treatment type for the remainder of the study. Research personnel will verify the treatment drug provided at the start of each study cycle.

10.6.2 BREAKING THE STUDY BLIND/PARTICIPANT CODE

In the event of a life-threatening medical necessity, death, or provider request for treatment consideration, the PI may request the unblinding of a study participant. The PI will contact the drug sponsor, Clovis Oncology, to break the blind in order to report to the required local and federal agencies as requested.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

FDA law and regulations require the collection and maintenance of complete clinical study data. This includes information on subjects who withdraw from a clinical investigation, whether the

subject decides to discontinue participation in the clinical trial (21 CFR 50.25(a)) or is discontinued by the investigator because the subject no longer qualifies under the protocol (for example, due to a significant adverse event or due to failure to cooperate with study requirements). FDA recognizes that a subject may withdraw from a study; however, the withdrawal does not extend to the data already obtained during the time the subject was enrolled. FDA's longstanding policy has been that all data collected up to the point of withdrawal must be maintained in the database and included in subsequent analyses, as appropriate.

All study documentation should remain on study site in a secured area with limited access.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Clovis, whichever is longer.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Clovis.

11.1 RESEARCH ELECTRONIC DATA CAPTURE

All study data should be entered in the electronic data capture. For this study the electronic data capture will be supported by REDCap. Prior to the start of trial, site investigators and research staff must complete REDCap in-service provided by the University of Colorado Denver. The study site will maintain documentation of REDCap training for each person approved for accessing REDCap. Access will then be granted by the University of Colorado. Site personnel with REDCap access will be able to maintain study records with review and edit permission.

11.2 DATA MANAGEMENT

All data entered into the REDCap database will be maintained by the host site for the REDCap database, the University of Colorado Denver. The University of Colorado research staff will review the database for completion of data and data inconsistencies and request resolution by the appropriate site. The University of Colorado will be responsible for all export and analysis of study data. Any requests for data sharing will be considered after completion of study analysis.

11.3 CONFIDENTIALITY AND REPORTING OF RESULTS

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Research teams will maintain all records in a secure area

with limited access. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject. If requested, the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained.

11.4 RETENTION OF DATA

The clinical research records must be retained for a minimum of two years after the marketing application is approved for the drug for the indication for which it was being investigated. Alternatively, if no application will be filed or if the application is not approved for the requested indication, the records must be retained for a minimum of two years after the investigation is discontinued and FDA is notified. 21 CFR §312.62(c)

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by IRB before the changes are implemented to the study. All changes to the consent form will IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating PIs, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Denver research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Denver.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Stored human samples will include archived tumor and genomic DNA samples. Archived tumor and germ line DNA samples will be used for genomic testing. Genetic testing data will be used in the exploratory analysis examining tumor genetics and disease response.

13.5 FUTURE USE OF STORED SPECIMENS

Biospecimens for this study will be stored at the University of Colorado Biorepository Core Facility. If there are remaining specimens after research is concluded for this study, specimens will be banked for additional future research at the University of Colorado Biorepository Core Facility. Participants will provide informed consent for this long-term storage and future research use. During the conduct of the study, an individual participant can withdraw consent to have biospecimens stored for future research. However, withdrawal of consent with regard to

biospecimen storage will not be possible after the study is completed. Specimens for future research will be provided in a deidentified manner and will be stripped of any patient and/or study identifiers.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, am encrypted, web-based data capture system provided by the University of Colorado Clinical and Translational Sciences Institute [25]. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations, or institution policies. No records will be destroyed without the written consent of the sponsor, if applicable.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

All deviations must be addressed in study source documents, reported to the local IRB, coordinating site/sponsor and DSMB. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the - SOP and/or study procedures manual.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

This study will be led by the principal investigator Bradley R. Corr, MD from the University of Colorado Denver; Aurora, CO 80045. Any questions in regards to the study leadership and oversight should be directed to them.

16 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

17 LITERATURE REFERENCES

1. Fleming, G.F., et al., *Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study.* J Clin Oncol, 2004. **22**(11): p. 2159-66.
2. Mutter, G.L., et al., *Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers.* J Natl Cancer Inst, 2000. **92**(11): p. 924-30.
3. Annunziata, C.M. and J. O'Shaughnessy, *Poly (ADP-ribose) polymerase as a novel therapeutic target in cancer.* Clin Cancer Res, 2010. **16**(18): p. 4517-26.
4. Ledermann, J., et al., *Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.* N Engl J Med, 2012. **366**(15): p. 1382-92.
5. Swisher, E.M., et al., *Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial.* Lancet Oncol, 2017. **18**(1): p. 75-87.
6. Mirza, M.R., et al., *Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.* N Engl J Med, 2016. **375**(22): p. 2154-2164.
7. Pujade-Lauraine, E., et al., *Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.* Lancet Oncol, 2017. **18**(9): p. 1274-1284.
8. Coleman, R.L., et al., *Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2017. **390**(10106): p. 1949-1961.
9. Iglehart, J.D. and D.P. Silver, *Synthetic lethality--a new direction in cancer-drug development.* N Engl J Med, 2009. **361**(2): p. 189-91.
10. Shen, W.H., et al., *Essential role for nuclear PTEN in maintaining chromosomal integrity.* Cell, 2007. **128**(1): p. 157-70.
11. Dedes, K.J., et al., *PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors.* Sci Transl Med, 2010. **2**(53): p. 53ra75.
12. Forster, M.D., et al., *Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer.* Nat Rev Clin Oncol, 2011. **8**(5): p. 302-6.
13. Ossovskaya, V., et al., *Upregulation of Poly (ADP-Ribose) Polymerase-1 (PARP1) in Triple-Negative Breast Cancer and Other Primary Human Tumor Types.* Genes Cancer, 2010. **1**(8): p. 812-21.
14. Ghabreau, L., et al., *Poly(ADP-ribose) polymerase-1, a novel partner of progesterone receptors in endometrial cancer and its precursors.* Int J Cancer, 2004. **109**(3): p. 317-21.
15. Miller, D., et al., *Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study.* Gynecologic Oncology, 2012. **125**(3): p. 771-771.
16. Muggia, F.M., et al., *Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study.* J Clin Oncol, 2002. **20**(9): p. 2360-4.
17. Audeh, M.W., et al., *Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial.* Lancet, 2010. **376**(9737): p. 245-51.
18. Gelmon, K.A., et al., *Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study.* Lancet Oncol, 2011. **12**(9): p. 852-61.
19. Ledermann, J., et al., *Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm).* Journal of Clinical Oncology, 2013. **31**(15_suppl): p. abstract 5505.
20. Mateo, J., et al., *DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.* N Engl J Med, 2015. **373**(18): p. 1697-708.
21. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

22. Lolas Hamameh, S., et al., *Genomic analysis of inherited breast cancer among Palestinian women: Genetic heterogeneity and a founder mutation in TP53.* Int J Cancer, 2017. **141**(4): p. 750-756.
23. Kim, G., et al., *FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy.* Clin Cancer Res, 2015. **21**(19): p. 4257-61.
24. Institute, N.C., *Common Terminology Criteria for Adverse Events, Version 4.03Common Terminology Criteria for Adverse Events, Version 4.03*. 2010.
25. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

18 APPENDICES

Version	Date	Significant Revisions