Clinical Study Protocol: CO-338-052

Study Title:	TRITON2: A Multicenter, Open-label Phase 2 Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency
Study Number:	CO-338-052
Study Phase:	Phase 2
Product Name:	Rucaparib (CO-338)
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Indication:	Metastatic castration-resistant prostate cancer
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted]
Responsible Medical Officer:	[redacted]

Protocol Version	Date
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Amendment 4:	24 August 2020

PROTOCOL APPROVAL SIGNATURE PAGE

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Date: 24 August 2020

Version: Amendment 4

Reviewed and Approved by:

PROTOCOL ACCEPTANCE FORM

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I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature	Date (dd Month yyyy)
Name (printed)	

1 SYNOPSIS

Sponsor Clovis Oncology, Inc.
Name of Finished Product Rucaparib tablets
Name of Active Ingredient Rucaparib camsylate (CO-338)
Study Title TRITON2: A Multicenter, Open-label Phase 2 Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency
Study Number CO-338-052
Study Phase Phase 2
Study Contact Information: This is a multicenter study. Information on investigators, institutions, and laboratories involved in the trial are maintained in the clinical study file and can be provided upon request. Contact information for the sponsor's medical and other study-related personnel are available in the Study Reference Binder.
Rationale Deoxyribonucleic acid (DNA) is constantly damaged by both endogenous and exogenous (environmental) assaults. Normal cells repair single-strand breaks (SSBs) in DNA through a process known as base excision repair (BER).[1] While there are several variations of BER, all pathways rely on the activity of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn repaired by homologous recombination repair (HRR) of the DNA, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2), as well as RAD51, Fanconi anemia core complex, ataxia telangiectasia mutated serine/threonine kinase (ATM) and ataxia telangiectasia and RAD3-related (ATR) protein, among others.[1] Homologous recombination defects or PARP inhibition on their own can be overcome by a cell, but the combination is fatal, a concept termed "synthetic lethality", and which forms the basis of the therapeutic approach of using PARP inhibition to kill cancer cells with a HR-deficient background.[1-3] Prostate cancer is the most common malignancy among men in the United States, and the second-most common cause of cancer-related mortality, with approximately 30,000 men dying of the disease each year.[4] Based upon GLOBOCAN 2012 estimates, prostate cancer is the 2nd leading malignancy diagnosis and 5th leading cause of death from cancer in men worldwide, with 307,000 deaths estimated in 2012.[5] The course of prostate cancer from diagnosis to death is often a series of clinical states progressing from localized disease to metastatic

castration-resistant prostate cancer (mCRPC), a disease state characterized by resistance to standard androgen deprivation therapies (ADT) and that accounts for the majority of prostate cancer deaths.

Homologous recombination deficiency (HRD) has been observed in many carcinomas, including prostate cancer. Men with a germline mutation in BRCA2 are at increased risk for developing prostate cancer, estimated at 2.5 to 8.6-fold compared with non-carriers.[6] Men with prostate cancer and a germline mutation in BRCA2 typically develop disease at a younger age, have more aggressive features and higher mortality rates. While less common in prostate cancer, germline mutations in BRCA1 are also associated with more aggressive disease.[7] In addition to germline mutations in BRCA1/2, somatic mutations in BRCA1/2 and other HRR genes eg, ATM, FANCA) have been shown to occur in advanced prostate cancer, suggesting that a significant percentage of patients with mCRPC may benefit from approaches exploiting a deficiency in HRR, such as a PARP inhibitor (PARPi).[8] A recent clinical study reported that 16 of 49 evaluable patients with advanced heavily pre-treated mCRPC had a response to the PARPi olaparib. Among the 16 evaluable patients in this study with HRR gene mutations, 14 (88%) had a response. Consistent with previous findings, gene mutations were most commonly observed in BRCA2 and ATM, but responses were observed in patients with mutations in these and other genes, including PALB2 and CHEK2.[9] These findings provide compelling evidence for use of a PARPi in a selected population of CRPC patients with predicted loss-of-function mutations in HRR genes, including BRCA1/2 and ATM.

Androgen deprivation therapy is the standard first-line systemic treatment for metastatic prostate cancer. It is highly active with clinical, radiological and prostate-specific antigen (PSA) responses for most patients – but almost all men will eventually progress to mCRPC. Over the last 10 years, multiple therapies have been shown to confer a survival benefit for patients with mCRPC and were approved on this basis, including docetaxel, cabazitaxel, Sipuleucel-T, radium Ra 223 dichloride, and 2 agents that target the androgen receptor (AR) pathway, abiraterone acetate and enzalutamide.[10-14] More recently, abiraterone has demonstrated a survival advantage for patients with metastatic high-risk castration-sensitive prostate cancer,[15] and in separate studies, both enzalutamide and apalutamide have demonstrated improvement in metastasis-free survival in patients with non-metastatic castration-resistant prostate cancer.[16, 17] Based on their tolerability and proven efficacy in the pre-chemotherapy setting, abiraterone acetate and enzalutamide are often used as first-line therapies for mCRPC; however, patients progress on these agents after a median duration of 16-18 months on treatment. Some patients receive a second regimen of AR-directed therapy; however, response rates are low in this setting.[18-21] For many patients who have progressed on AR-directed therapy, systemic chemotherapy is the next treatment option. Treatment options include docetaxel (75 mg/m^2 every 3 weeks) plus prednisone, cabazitaxel plus prednisone, radium Ra 223 dichloride, and sipuleucel-T. The two latter agents are generally well-tolerated and thus reasonable treatment options for patients prior to receiving treatment with chemotherapy or for patients with bone-only disease.

Despite clinical benefit from AR-directed therapy and chemotherapy, mCRPC patients eventually develop progressive disease. Novel therapies that provide robust clinical benefit and have a good safety profile are still needed for patients with advanced mCRPC, and a targeted therapy such as a PARPi for the subset of patients who exhibit features of HRD represents an attractive option.

Primary Objective:

- To assess the efficacy of rucaparib based on the response rate in mCRPC patients with HRD who progressed on AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) and taxane-based chemotherapy in the castration-resistant setting

Secondary Objectives:

- To assess duration of response (DOR)
- To assess radiologic PFS (rPFS)
- To assess overall survival (OS)
- To assess clinical benefit rate (CBR)
- To assess PSA response ≥ 50% (all patients)
- To assess PSA response ≥ 90% (all patients)
- To assess time to PSA progression
- To characterize the steady-state pharmacokinetics (PK) of rucaparib in mCRPC patients
- To assess safety and tolerability

Exploratory Objectives:

- To evaluate Patient-reported Outcome (PRO) using the EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L), Functional Assessment of Cancer Therapy – Prostate (FACT-P), analgesic drug score, and Brief Pain Inventory – Short Form (BPI-SF) instruments
- To assess changes in the molecular profile over time of matched pre and post-treatment tumor or plasma samples
- To assess concordance in HRR gene mutation status in matched Pre-Screening biopsy tissue, archival primary and metastatic tumor tissue, and plasma circulating tumor DNA (ctDNA)
- To assess ctDNA as a molecular marker of response
- To assess time to first subsequent antineoplastic therapy
- To evaluate loss of heterozygosity (LOH) in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples
- To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples.

Study Design

This is a Phase 2 multicenter study evaluating rucaparib for treatment of patients with mCRPC whose tumors are associated with HRD. This study will enroll mCRPC patients with deleterious mutations in BRCA1/2, ATM, or other HRR genes associated with sensitivity to PARPi (Appendix 1). All patients will be required to have progressed on prior AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) after receiving treatment with at least 1, but no more than 2, of these agents. Patients must also have progressed after 1 prior line of taxane-based chemotherapy for mCRPC. Patients who received prior PARPi treatment, mitoxantrone, cyclophosphamide or platinum-based chemotherapy will be excluded.

This study consists of a Pre-Screening Phase, Screening Phase, Treatment Phase, and

Post-Treatment Phase. Patients will receive rucaparib monotherapy in the Treatment Phase, and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study.

Pre-Screening Phase

The purpose of the Pre-Screening Phase is to perform central plasma and tumor tissue testing to identify patients with qualifying deleterious HRR gene mutations. If a patient has an eligible deleterious mutation in a HRR gene identified from local testing, the Pre-Screening Phase is not required and the patient should proceed to the Screening Phase.

To enter the Pre-Screening Phase, patients should have evidence of radiographic or biochemical disease progression, and be eligible for this study as their immediate next therapy. Patient tissue and plasma samples should be submitted simultaneously during Pre-Screening. Tissue submitted for Pre-Screening testing should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy and the patient consents to this procedure. A biopsy or resection of a visceral or nodal site of metastasis is preferred; however, biopsy of primary tumor or of a site of bony metastasis is also acceptable. If a metastatic biopsy is not feasible, archival tissue samples should be submitted, if available. To reduce the chance of test failure, archival tissue should be < 3 years old.

Screening Phase

The purpose of the Screening Phase is to perform study-specific screening assessments, other than testing for qualifying deleterious HRR gene mutations. All patients must have a deleterious mutation in BRCA1/2, ATM, or other HRR genes associated with sensitivity to PARPi (Appendix 1) in order to enter the Screening Phase. Mutations may be identified by local testing, or through central testing provided by the sponsor during the Pre-Screening Phase. For local test results, the classification of the mutation as deleterious must be documented in the patient's medical record.

Treatment Phase

Rucaparib will be administered at a starting dose of 600 mg BID. Tumor assessments by CT/MRI and bone scans will be performed during screening, at the end of every 8 calendar weeks (±7 days) from Study Day 1 (Week 1) up to 24 weeks and every 12 calendar weeks (±7 days) thereafter, and at the Treatment Discontinuation Visit, if applicable. Modified RECIST Version 1.1 criteria will be used to document radiologic response in soft tissue (visceral and nodal) disease and Prostate Cancer Working Group 3 (PCWG3) criteria will be used to document radiologic progression in bone lesions. Any drug modifications (interruption, dose reduction, or discontinuation) should be documented in the eCRF and source documents. If study treatment is interrupted, tumor assessments will not be delayed and will proceed on the regular study schedule. Copies of all radiologic scans will be collected for central independent radiology review (IRR).

Patients will receive rucaparib until confirmed radiologic disease progression assessed by investigator based on modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up; or withdrawal of consent. PSA rise without evidence of confirmed radiologic progression is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to

start a new systemic antineoplastic therapy throughout the study. Palliative radiation for treatment of painful bony metastases and initiation of bisphosphonates or other approved bone-targeting agents are allowed and should not result in discontinuation of study drug therapy.

If a patient has radiologic progression, but continues to derive clinical benefit per the investigator, then continuation of treatment beyond progression may be requested by investigator. In such cases, the decision to continue will be made jointly between the investigator and the sponsor (or designee), and the patient must consent prior to continuing treatment with rucaparib.

Safety data will be periodically reviewed by Data Monitoring Committee (DMC). The DMC will comprise study investigators and sponsor representatives. The DMC will meet after the first 20 patients received rucaparib for at least 28 days or discontinued study treatment, and then at least semi-annually.

Post-treatment Phase

Upon treatment discontinuation, patients will have a Treatment Discontinuation Visit, a 28-Day Follow-up Visit, and then will proceed to long-term follow-up. An optional tumor biopsy will be collected prior to the start of subsequent anticancer therapy from patients who experience radiographic or unequivocal clinical disease progression and provide appropriate consent.

If treatment was discontinued for reasons other than radiologic disease progression, radiologic tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) and PRO assessments will continue until confirmed radiographic disease progression.

Ongoing serious adverse events (SAEs), adverse events of special interest (AESIs), and treatment related Grade 3/4 adverse events (AEs) will be followed until either resolution or stabilization has been determined or until lost to follow-up. After the 28-Day Follow-up Visit, only SAEs considered as potentially related to study drug should be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Follow-up Visit, AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the 28-Day Follow-up Visit (28-days after the last dose of rucaparib).

All patients will be followed for survival and subsequent treatments every 12 weeks (± 14 days) relative to the last dose of rucaparib until death, loss to follow-up, withdrawal of consent, or study closure.

Number of Patients

The total enrollment planned for this study is approximately 360 patients across 3 cohorts as follows:

- Cohort A will include up to 100 patients with a deleterious BRCA1/2 mutation who have measurable visceral and/or nodal disease (with a maximum of 60 patients who have only measurable lymph node disease), and up to approximately 50 patients with a deleterious ATM mutation who have measurable visceral and/or nodal disease
- Cohort B will include up to approximately 100 patients with a deleterious BRCA1/2 mutation and up to approximately 50 patients with a deleterious ATM mutation who do not have measurable visceral and/or nodal disease
- Cohort C will include up to approximately 60 patients with or without measurable visceral and/or nodal disease who have a deleterious mutation in a HRR gene other than BRCA1/2 or ATM.

Number of Sites

Patients will be enrolled across approximately 150 sites worldwide.

Inclusion Criteria

All patients enrolling into the study must meet all of the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-specific evaluation
2. Male ≥ 18 years of age at the time the informed consent form is signed
3. Have a histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate (pure small-cell histologies or pure high-grade neuroendocrine histologies are excluded; neuroendocrine differentiation is allowed) that is metastatic
4. Surgically or medically castrated, with serum testosterone levels of ≤ 50 ng/dL (1.73 nM). For patients currently being treated with luteinizing hormone–releasing hormone (LHRH) analogs (ie, patients who have not undergone an orchiectomy), therapy must be continued throughout the study
5. Evidence of disease progression after prior therapy for prostate cancer:
    a. Disease progression after treatment with at least 1 but no more than 2 prior next-generation AR-targeted therapies (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent); treatment with the older anti-androgen therapies such as bicalutamide, flutamide, and nilutamide are not counted toward this limit,

    AND

    b. Disease progression after treatment with 1 prior line of taxane-based chemotherapy for castration-resistant disease. Prior taxane therapy administered for hormone-sensitive disease is permitted and is not counted toward this limit.
6. Disease progression after initiation of most recent therapy is based on <u>any</u> of the following criteria:

a. Rise in PSA: a minimum of 2 consecutive rising levels, with an interval of ≥ 1 week between each determination. The most recent screening measurement must have been ≥ 2 ng/mL
b. Transaxial imaging: new or progressive soft tissue masses on CT or MRI scans as defined by RECIST 1.1
c. Radionuclide bone scan: at least 2 new metastatic lesions

7. Patients in Cohorts A and B must have a deleterious mutation in BRCA1/2 or ATM
   Patients in Cohort C must have a deleterious mutation in another HRR gene associated with sensitivity to PARPi (Appendix 1)
   Mutations may be identified by local testing, or through central testing by the sponsor of plasma or tumor tissue. For local test results, the classification of the mutation as deleterious must be documented in the patient's medical record
8. Patients in Cohort A must have measurable visceral or nodal disease per RECIST v1.1 criteria (Appendix 2)
   Patients in Cohorts B and C (without measurable disease) must have PSA ≥ 2 ng/mL on the most recent measurement
9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix 3)
10. Have adequate organ function confirmed by the following clinical laboratory values obtained within 14 days prior to the first dose of rucaparib:
    a. Bone Marrow Function
       i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
       ii. Platelets > 100×10^9/L
       iii. Hemoglobin ≥ 10 g/dL independent of transfusion within 14 days
    b. Hepatic Function
       i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN
       ii. Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
    c. Renal Function
       i. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft-Gault formula
11. Male patients who are committed to undertaking the following measures for the duration of the study and after the last dose of rucaparib for the time period specified:
    a. Use a condom during sex while being treated and for 3 months after the last dose of rucaparib,
    b. Do not make semen donations during treatment and for 3 months after the last dose of rucaparib,
    c. Those with female partners of childbearing potential may be enrolled if they are:
       i. Documented to be surgically sterile (ie, vasectomy);

ii. Committed to practicing true abstinence during treatment and for 3 months after the last rucaparib dose; or
iii. Committed to using an effective method of contraception (refer to protocol) with their partner during treatment and for 3 months following the last dose of rucaparib

12. Have a life expectancy of at least 6 months

Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply:

1. Active second malignancy, with the exception of curatively treated non-melanoma skin cancer, carcinoma *in situ*, or superficial bladder cancer
   - Patients with a history of malignancy that has been completely treated, and currently with no evidence of that cancer, are permitted to enroll in the trial provided all therapy was completed > 6 months prior and/or bone marrow transplant (BMT) > 2 years prior to first dose of rucaparib
2. Prior treatment with any PARP inhibitor, mitoxantrone, cyclophosphamide or any platinum-based chemotherapy
3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic, previously treated CNS metastases are eligible provided they have been clinically stable (not requiring steroids for at least 4 weeks prior to first dose of rucaparib) and have had appropriate scans at screening assessment
4. Symptomatic or impending spinal cord compression unless appropriately treated, clinically stable, and asymptomatic
5. Pre-existing duodenal stent and/or any gastrointestinal (GI) disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C
7. Received treatment with chemotherapy, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs within < 2 weeks prior to first dose of rucaparib. Treatment with hormonal therapies (with the exception of LHRH analog) must be discontinued at least 7 days prior to the first dose of rucaparib
8. Adverse effect of prior therapy not resolved to CTCAE Grade 1 or below with the exception of alopecia. Ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from the sponsor
9. Initiated low-dose corticosteroid, bisphosphonate, or denosumab therapy or adjusted low-dose corticosteroid, bisphosphonate, or denosumab dose/regimen within < 4 weeks prior to first dose of rucaparib. Patients on a stable low-dose corticosteroid, bisphosphonate, or denosumab regimen are eligible and may continue treatment

10. Non-study related minor surgical procedure within < 5 days, or major surgical procedure within < 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study

Study Treatment

The starting dose and schedule of rucaparib is 600 mg ingested twice a day (BID). Patients may take rucaparib with or without food. Each dose should be taken with at least 8 oz (240 mL) of water as close to 12 hours apart as possible, preferably at the same times every day. Rucaparib will be provided as 200, 250, and 300 mg dose strength tablets. Tablets should be swallowed whole.

Dose holds or reductions are permitted in the event of unacceptable toxicity.

Patients will receive rucaparib until confirmed radiologic disease progression as assessed by investigator using modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, or withdrawal of consent. However, if a patient receiving rucaparib has met criteria for confirmed radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 criteria, but the patient continues to derive clinical benefit per the investigator, then continuation of treatment will be permitted with additional consent.

Concomitant Medications

During the study, supportive care (eg, antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. Supportive care must be recorded for each patient in the appropriate section of the eCRF.

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered per standard of care and according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

Palliative radiotherapy for the treatment of painful bony metastasis is permitted during the study. Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation-related toxicity.

For patients who have not undergone an orchiectomy and are currently being treated with luteinizing hormone-releasing hormone (LHRH) analogs at the time of consent, therapy must be continued throughout the study.

No other anticancer therapies (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study with the exception of LHRH analogs and palliative radiotherapy for painful bony metastases.

Initiation of bisphosphonates or other approved bone targeting agents if clinically indicated is allowed, and should not result in study treatment discontinuation unless patient has radiographic evidence of disease progression.

Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions.

Based on the results from the cytochrome P450 (CYP) interaction clinical study CO-338-044, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on P-gp. Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes with narrow therapeutic windows. 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. Patients taking warfarin should have international normalized ratio (INR) monitored regularly according to standard institutional practices, and those patients taking phenytoin should have therapeutic drug level monitored.

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.

Treatment Discontinuation Criteria

A patient must be discontinued from treatment with study drug if any of the following apply:

- confirmed radiologic disease progression as assessed by investigator using modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria;
- unequivocal clinical disease progression;
- unacceptable toxicity or inability to tolerate further treatment;
- loss to follow-up; or
- withdrawal of consent.

Efficacy Assessments

Soft tissue (visceral and nodal) disease will be evaluated for evidence of radiographic response based on modified RECIST 1.1 criteria (Appendix 2). Bone lesions will be followed and evaluated for evidence of radiologic progression based on PCWG3 criteria (Appendix 2). Additionally, PSA response will be evaluated.

Tumor assessments will be performed during screening (baseline), at the end of every 8 calendar weeks (± 7 days) relative to Study Day 1 (Week 1) up to 24 weeks, then every 12 calendar weeks (± 7 days), until confirmed radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, as assessed by the investigator, loss to follow-up, withdrawal, or study closure. Tumor assessments should be performed at the time of treatment discontinuation, at the 28-day Follow-up visit, or during Long-term Follow-up if the reason was other than radiologically confirmed disease progression and it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment. Tumor assessments should continue on schedule (ie, every 8 or 12 weeks) during Long-term Follow-up until radiographically confirmed disease

progression. If a complete response (CR) or partial response (PR) is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented.

Tumor assessments should consist of clinical examination and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (MRI, X-ray, PET/CT, and ultrasound) may also be performed if required. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. Radionuclide bone scanning (whole body) should be performed using 99mTc-methylene diphosphonate (MDP) or hydroxydiphosphonate (HDP). All sites of disease should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time.

Copies of CT scans (and other imaging, as appropriate) will be collected from all patients for IRR.

Safety Assessments

Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, and severity of AEs reported;
- Clinical laboratory investigations (hematology, serum chemistry, urinalysis);
- Vital signs (blood pressure, heart rate, and body temperature);
- 12–lead ECGs;
- Physical examinations; and
- ECOG performance status.

Statistical Methods

Sample Size Justification and Interim Analysis

The enrollment planned for this study is approximately 360 patients, with up to approximately 150 patients in Cohort A with measurable visceral and/or nodal disease (ie, up to 100 patients with a deleterious BRCA1/2 mutation [with a maximum of 60 patients who have only measurable lymph node disease], and up to approximately 50 patients with a deleterious ATM mutation), up to approximately 150 patients in Cohort B (ie, up to approximately 100 patients with a deleterious BRCA1/2 mutation and 50 patients with a deleterious ATM mutation), and up to approximately 60 patients in Cohort C.

Cohort A

Cohort A will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort A (BRCA1/2)

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. With rolling enrollment, after the first 37 patients with a deleterious BRCA1/2 mutation have either: a) completed 16 weeks of treatment or b) discontinued treatment prior to completing, an interim analysis will be performed (ie, Stage 1). If ≤ 8/37 patients in Stage 1 have a confirmed objective response (CR or PR per

investigator and without progression in bone per PCWG3), the DMC will evaluate the overall benefit/risk for patients with deleterious BRCA1/2 mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 9/37 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. With 83 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

If there are at least 23 responses in 83 patients with a deleterious BRCA1/2 mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 90% when the true response rate is 35%.

Note: If the study is to proceed to Stage 2, additional patients with a deleterious BRCA1/2 mutation up to 100 total patients (and a maximum of 60 patients with only measurable lymph node disease) will be enrolled in Cohort A (BRCA1/2) if additional clinical data is requested by the regulatory authorities to support regulatory filing. If sufficient evidence exists to support a regulatory filing prior to fully enrolling Cohort A (BRCA1/2), enrollment may be discontinued early.

Cohort A (ATM)

Patients in Cohort A (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort A (BRCA1/2). It is expected that about 1/3 of the Cohort A patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort A (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort A (ATM).

A Simon 2-stage type futility rule will be employed in Cohort A (ATM). An interim analysis (Stage 1) will be performed after the first 31 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 6/31 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 7/31 patients have a confirmed objective response, then enrollment will continue in Stage 2. With 53 total patients with a deleterious ATM mutation, characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

If there are at least 16 responses in 53 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 80% when the true response rate is 35%.

Cohort B

Cohort B will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM). Cohort B will be enrolled concurrently with Cohort A and is expected to enroll at approximately the same rate as Cohort A. Enrollment in Cohort B will be halted when Cohort A (BRCA1/2) is fully enrolled. Therefore, it is anticipated that up to approximately 150 patients may be enrolled in Cohort B.

Cohort B (BRCA1/2)

A Simon 2-stage type futility rule will be employed in Cohort B (BRCA1/2). An interim analysis (Stage 1) will be performed after the first 19 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 4/19 patients in Stage 1 have a PSA response (≥ 50% decrease), the DMC will evaluate the overall benefit/risk for patients with deleterious BRCA1/2 mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 5/19 patients have a PSA response, then enrollment will continue in Stage 2. With 54 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 16 responses in 54 patients with a deleterious BRCA1/2 mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 90% when the true response rate is 40%. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 100 total, may be enrolled. Enrollment in Cohort B (BRCA1/2) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (ATM)

Patients in Cohort B (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort B (BRCA1/2). It is expected that about 1/3 of the Cohort B patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort B (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort B (ATM).

A Simon 2-stage type futility rule will be employed in Cohort B (ATM). An interim analysis (Stage 1) will be performed after the first 18 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 4/18 patients in Stage 1 have a PSA response (≥ 50% decrease), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 5/18 patients have a PSA response, then enrollment will continue in Stage 2. With 33 total patients with a deleterious ATM mutation, characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 11 responses in 33 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) will be rejected. This design yields a type I error rate of 5% and power of 80% when the true response rate is 40%. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 50 total, may be enrolled. Enrollment in Cohort B (ATM) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort C

Up to approximately 60 patients will be enrolled into Cohort C. Enrollment in Cohort C will be halted when Cohort A (BRCA1/2) is fully enrolled. Since this cohort will enroll patients that have 1 of several different deleterious HRR gene mutations, each gene will be examined separately. It is anticipated that < 6 patients will have a deleterious mutation in the same HRR gene; however, if enrollment of patients with a deleterious mutation in the same gene is higher than anticipated then enrollment will be held at 6 patients with any 1 deleterious gene mutation and a futility rule will be implemented such that if no responses are observed, then enrollment of patients with a deleterious mutation in that particular gene will be stopped, in consultation with the DMC.

Primary Efficacy Analysis:

Cohort A: The primary endpoint is ORR as assessed by central IRR and analyzed separately for patients with deleterious BRCA1/2 and ATM mutations. ORR for Cohort A is defined as the proportion of patients with a confirmed response of CR or PR using modified RECIST Version 1.1 (ie, CR or PR by IRR assessment and no progression in bone per PCWG3 by IRR assessment).

Cohort B: The primary endpoint is PSA response (≥ 50% decrease) as assessed by a local laboratory and analyzed separately for patients with deleterious BRCA1/2 and ATM mutations. The proportion of patients with ≥ 50% PSA decrease from baseline will be reported.

Cohort C: The primary endpoint is ORR defined as the proportion of patients with a confirmed response of CR or PR using either modified RECIST Version 1.1 (if measurable visceral and/or nodal disease is present) or ≥ 50% PSA decrease from baseline (if visceral and/or nodal disease is absent). For patients with measurable disease, response will be assessed by central IRR.

Secondary Efficacy Analyses:

Duration of response is defined as the time from the date that a response (modified RECIST Version 1.1 or PSA ≥ 50%) is first reported to the time that progression (using modified RECIST Version 1.1/PCWG3 criteria or PSA-progression criteria, respectively) is documented.

Radiologic PFS (rPFS) is defined as the time from first dose of rucaparib to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) or death due to any cause, whichever occurs first. Radiologic disease progression includes confirmed bone disease

progression and soft tissue disease progression adjudicated by independent central radiological review using the PCWG3 guidelines for bone disease and modified RECIST Version 1.1 for soft tissue disease.

OS is defined as the date from first dose of rucaparib to the date of death due to any cause.

CBR is defined as the combination of CR, PR, and SD as defined by modified RECIST Version 1.1 with no progression in bone per PCWG3 criteria. Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline to lowest post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later. PSA response will be calculated for all patients with PSA values at baseline and at least 1 post-baseline assessment. PSA will be assessed by a local laboratory.

Time to PSA progression is defined as the time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline value for patients who did not have a decline in PSA) in PSA was measured. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later.

Safety Analyses

Adverse events (AEs), clinical laboratory results, vital signs, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized. AEs will be summarized overall and separately for SAEs, AESIs, AEs leading to discontinuation, AEs leading to death, and Grade 3 or higher AEs graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized categorically.

A DMC will review safety and efficacy data on a periodic basis to ensure an acceptable overall risk and benefit for patients participating in the study.

Date of Protocol Amendment 4 Approval

24 August 2020

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

99m Tc MDP	99m technecium methyl disphosphonate
ADP	adenosine diphosphate
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALCOA+	Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and 'Plus' (+) Complete, Consistent, Enduring, and Available
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated serine/threonine kinase
ATR	ataxia telangiectasia and RAD3-related
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice daily
Bp	base-pair
BPI-SF	Brief Pain Inventory – Short Form
BRCA	breast cancer 1 or breast cancer 2
BRCA1/2	breast cancer gene 1 or breast cancer gene 2
BMT	bone marrow transplant
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
CL/F	apparent total clearance of drug after oral administration
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRM	continual reassessment model
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CT	computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
CV	coefficient of variation
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicities
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand breaks
EC	European Commission
EC_{50}	concentration producing 50% of maximum effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EQ-5D-5L	EuroQol 5 dimensions 5 level questionnaire
EU	European Union
F	Bioavailability
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FD & C	colorants that have been approved by the Food and Drug Administration for use in food, drugs and cosmetics
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FMI	Foundation Medicine, Inc.
FSH	follicle stimulating hormone
FTC	fallopian tube cancer
gBRCA	germline breast cancer gene 1 or 2 mutation
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GLP	Good Laboratory Practice
H & E	hematoxylin and eosin
HDP	hydroxydiphosphonate
HDPE	high-density polyethylene
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose

HGSOC	high-grade serous ovarian cancer
HNSTD	highest non-severely toxic dose
HPLC	high-performance liquid chromatography
HR	hazard ratio
Hr	hour
HRD	homologous recombination deficiency
HRR	homologous recombination repair
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IRR	independent radiological review
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IWRS	Interactive Web Response System
IV	Intravenous
K_i	inhibition constant
K_{ic}	inhibition constant competitive
LHRH	luteinizing hormone-releasing hormone
LOH	loss of heterozygosity
MATE	multidrug and toxin extrusion transporter
mCRPC	metastatic castration-resistant prostate cancer
MDP	methylene diphosphonate
MDR1	multidrug resistance protein 1
MDS	myelodysplastic syndrome
MRI	magnetic resonance imagiing
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MS	mass spectrometry
MTD	maximum tolerated dose
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
OAT	organic ion transporter
OCT	organic cation transporter

ORR	objective response rate
OS	overall survival
P_{app}	apparent permeability coefficient
PARP	poly(ADP-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease (in context of disease monitoring)
PDX	patient-derived xenograft
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLD	pegylated liposomal doxorubicin
PPC	primary peritoneal cancer
PR	partial response
PRO	Patient-reported Outcome
PSA	prostate-specific antigen
PV	pharmacovigilance
QD	once daily
RAD51C	RAD51 homolog C
RAD51D	RAD51 homolog D
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
rPFS	radiologic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
sBRCA	somatic breast cancer gene 1 or 2 mutation
SD	stable disease (in context of disease monitoring)
SOC	system organ class
SOP	Standard Operating Procedure
SSB	single-strand break
$t_{1/2}$	terminal half-life
tBRCA	tumor tissue mutation in BRCA1 or BRCA2, includes gBRCA and sBRCA
TEAE	treatment-emergent adverse event
T_{max}	time of occurrence of C_{max}
TMZ	Temozolomide
UGT	uridine diphosphate-glucuronosyl transferase
UK	United Kingdom
ULN	upper limit of normal

Upper case gene/protein names	Gene and protein names should be in italics and plain text, respectively, based on HUGO Gene Nomenclature Committee guidelines. However, in this document mutations which occur at both the gene and protein level are often discussed. Therefore for enhanced readability, gene and protein names are written in plain text
US	United States
USAN	United States Adopted Name
USP	US Pharmacopeia
V_{ss}	volume of distribution at steady-state
WBC	white blood cell
wt	wild-type

3 INTRODUCTION

3.1 Investigational Product

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 susceptibility gene 1 or 2 (BRCA1 or BRCA2) mutation in both clinical and nonclinical studies.

Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with metastatic castration-resistant prostate cancer (mCRPC) associated with HRD, including patients with a deleterious mutations in BRCA1, BRCA2 and ataxia telangiecstasia mutated serine/threonine kinase (ATM) and other homologous recombination repair (HRR) gene mutations.

3.2 Background and Rationale for PARP Inhibition

Deoxyribonucleic acid (DNA) is constantly damaged by both endogenous and exogenous (environmental) assaults. Endogenous causes include spontaneous base changes, replication errors, and oxygen-free radicals. Exogenous agents of DNA damage include chemicals and both ultraviolet (UV) and ionizing radiation. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs). Normal cells repair SSBs in DNA through a process known as base excision repair (BER).[1] While there are several variations of BER, all pathways rely on the activity of PARP enzymes. In humans, the PARP family encompasses 17 enzymes, of which PARP-1 is the best characterized.[22] SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn repaired by HRR of the DNA, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2), as well as RAD51, Fanconi anemia core complex, ataxia telangiectasia mutated serine/threonine kinase (ATM), and ataxia telangiectasia and RAD3-related (ATR) protein, among others.[1] Thus, HRR processes act as a functional buffer to enable normal cells to survive the effects of PARP and BER inhibition and overcome DSB in DNA. Homologous recombination defects or PARP inhibition on their own can be overcome by a cell, but the combination is fatal, a concept termed “synthetic lethality”, which forms the basis of the therapeutic approach of using PARP inhibition to kill cancer cells with HRD.[1-3]

3.3 Metastatic Castration-resistant Prostate Cancer

Prostate cancer is the most common malignancy among men in the United States, and the second-most common cause of cancer-related mortality, with approximately 30,000 men dying of the disease each year.[4] Based upon GLOBOCAN 2012 estimates, prostate cancer is the 2nd leading malignancy diagnosis and 5th leading cause of death in men worldwide, with 307,000 deaths estimated in 2012.[5] The course of prostate cancer from diagnosis to death is often a series of clinical states progressing from localized disease to mCRPC, a disease state characterized by resistance to standard androgen deprivation therapies and that accounts for the majority of prostate cancer deaths.

HRD has been observed in many carcinomas, including prostate cancer. Men with a germline mutation in BRCA2 are at increased risk for developing prostate cancer, estimated at 2.5 to 8.6-fold compared with non-carriers.[6] Men with prostate cancer and a germline mutation in BRCA2 typically develop disease at a younger age, have more aggressive features and higher mortality rates; while less common in prostate cancer, germline mutations in BRCA1 are also associated with more aggressive disease.[7] In addition to germline mutations in BRCA1/2, somatic mutations in BRCA1/2 and other HRR genes have been shown to occur in advanced prostate cancer.[8] A large genomic study of mCRPC identified a 12.7% rate of mutation/deletion in BRCA2 (of which over 90% was biallelic), half of which was a germline mutation in BRCA2; a 7% rate of loss of ATM, an approximately 5% mutation rate of CDK12, a previously reported positive regulator of BRCA genes, and lower rates of mutation of BRCA1, FANCA, RAD51B, RAD51C, and other HRR genes. Overall, almost 23% of tumors were found to have a mutation in at least one HRR gene, and over 19% of tumors had either a BRCA1/2 or ATM mutation, suggesting that in principle a significant percentage of patients with mCRPC may benefit from approaches exploiting a deficiency in HRR, such as a PARP inhibitor (PARPi).[8] A recent clinical study reported that 16 of 49 evaluable patients with advanced heavily pre-treated mCRPC had a response to the PARPi, olaparib. Response was defined as a RECIST partial response (PR) or complete response (CR), circulating tumor cell reduction from 5 or more to less than 5 per 7.5 ml of blood, or 50% decrease in PSA. Fourteen of the 16 responders had a mutation in a HRR gene, most commonly BRCA2 and ATM, but also other genes involved in DNA damage sensing and repair, including FANCA, PALB2, and CHEK2.[9] These findings provide compelling evidence for use of a PARP inhibitor in a selected population of CRPC patients with predicted loss-of-function mutations in HRR genes such as BRCA1/2 and ATM, as well as in HRR genes such as BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L where deleterious mutations have generally been observed at lower frequencies.

3.3.1 Treatment of Metastatic Castration-resistant Prostate Cancer

Androgen deprivation therapy (ADT) is the standard first-line systemic treatment for metastatic prostate cancer. It is highly active with clinical, radiological and PSA responses for most patients – but almost all men will eventually progress to CRPC. Over the last 10 years, multiple therapies have been shown to confer a survival benefit for patients with mCRPC and were approved on this basis, including docetaxel, cabazitaxel, Sipuleucel-T, radium Ra 223 dichloride, and 2 agents that target the androgen receptor (AR) pathway, abiraterone acetate and enzalutamide.[10-14, 16]. More recently, abiraterone has demonstrated a survival advantage for patients with metastatic high-risk castration-sensitive prostate cancer,[15] and in separate studies, both enzalutamide and apalutamide have demonstrated improvement in metastasis-free survival in patients with non-metastatic castration-resistant prostate cancer.[16, 17]

Based on their tolerability and proven efficacy in the pre-chemotherapy setting, abiraterone acetate and enzalutamide have become common first-line therapies for mCRPC; however, patients progress on these agents after a median duration of 16-18 months treatment. Response rates to a second regimen of AR-directed therapy are low,[18-21] therefore systemic chemotherapy is often considered as the next treatment option for patients who have progressed on AR-directed therapy. Docetaxel (75 mg/m^2 every 3 weeks) plus prednisone demonstrated good activity (45% PSA response rate and 19.2 months overall survival [OS]) in chemotherapy-naïve CRPC patients

who progressed on ADT, but has generally been replaced by abiraterone acetate and enzalutamide as first-line treatment for mCRPC. Docetaxel appears to be less effective in the post-abiraterone or enzalutamide setting, with median progression-free survival (PFS) of approximately 4.5 months.[19] It is also associated with significant toxicity, including Grade 3/4 neutropenia, fatigue, sensory neuropathy, fatigue, stomatitis, diarrhea and fatigue.[14] Cabazitaxel plus prednisone is a treatment option following docetaxel-based treatment based on demonstrated OS benefit versus mitoxantrone (median of 15.1 versus 12.7 months, HR = 0.70 (95% confidence interval [CI] 0.59-0.83, p<0.0001) in mCRPC patients who progressed on both ADT and docetaxel therapy, but it is also associated with significant Grade 3/4 neutropenia and diarrhea.[23] Radium Ra 223 dichloride received approval for treatment of mCRPC based on overall survival (OS) benefit (median of 14 versus 11.2 months for placebo) in patients who had bone, but not visceral disease.[24] Sipuleucel-T extended median OS in mCRPC- by 4.1 months compared to placebo,[25] but its effectiveness is not known in the post-abiraterone/enzalutamide and post-docetaxel setting. Both agents are generally well-tolerated and thus reasonable treatment options for patients prior to receiving treatment with chemotherapy or for patients with bone-only disease.

Nevertheless, novel therapies that provide robust clinical benefit and have a good safety profile are still needed for patients with advanced mCRPC, and a targeted therapy such as a PARPi for the subset of patients who exhibit features of HRD represents an attractive option.

3.4 Prior Experience with Rucaparib

An overview of data from nonclinical and clinical studies are provided below and described in detail and most currently in the rucaparib Investigator's Brochure (IB). A summary of the benefits and risks of rucaparib treatment are also provided in the rucaparib IB. The nonclinical and clinical data and benefits and risks of rucaparib have been consistent over time.

3.4.1 Nonclinical Experience with Rucaparib

The results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition.

Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3 and has robust and durable *in vitro* and *in vivo* activity in multiple BRCA1/2 mutant cell lines and xenograft models. Rucaparib was also active in a BRCA wild-type model, consistent with *in vitro* data suggesting that rucaparib is active in cells with other defects in HRR through synthetic lethality. *In vitro* screens suggested that rucaparib has a limited potential for off-target effects. Safety pharmacology studies suggest that when given orally, rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-gp and BCRP substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. *In vitro* data suggested slow metabolism by cytochrome P450 enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and

dogs. *In vitro*, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UDP-glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1), a weak inhibitor of OCT2, and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal (GI) systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an *in vitro* chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility.[26-29]

3.4.2 Clinical Experience with Rucaparib

Rucaparib has been evaluated in Phase 1, 2, and 3 clinical studies and is being evaluated in ongoing Phase 1, 2, and Phase 3 clinical studies. The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents. Initially, an IV formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts. The IV formulation is no longer in use.

On 19 December 2016, under priority and expedited review, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious breast cancer susceptibility gene (BRCA) mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with 2 or more chemotherapies and on 6 April 2018 Rubraca was approved for use as monotherapy maintenance treatment for adult patients with recurrent epithelial ovarian (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) who are in response (complete or partial) to platinum-based chemotherapy. On 29 May 2018, the European Commission (EC) authorized oral rucaparib as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.

Six studies (A4991002, A4991005, A4991014, CO-338-010, CO-338-023 [RUCAPANC], and CO-338-045 [ADME]) have been completed and 6 studies in addition to the one described in this protocol are ongoing (CO-338-014 [ARIEL3], CO-338-017 [ARIEL2], CO-338-043 [ARIEL4], CO-338-044 [DDI], CO-338-063 [Phase 3 mCRPC], and CO-338-078 [hepatic impairment study]).

Details of all completed, ongoing, and planned studies are described briefly below. Additional information is provided in the rucaparib IB.

Completed Studies

- A4991002: a Phase 1 open-label, dose-escalation study of IV rucaparib in combination with TMZ in patients with advanced solid tumors (Part 1) or malignant melanoma (Part 2).
- A4991005: a Phase 2, open-label study of IV rucaparib in combination with TMZ in patients with metastatic melanoma.
- A4991014: a Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in patients with an advanced solid tumor.
- CO-338-023 (RUCAPANC): a Phase 2, single-arm, open-label study of monotherapy oral rucaparib as treatment for patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious BRCA mutation.
- CO-338-010: 3-part, open-label, Phase 1/2 study of monotherapy oral rucaparib.
  - Part 1: a Phase 1 portion evaluating PK and safety of escalating doses of rucaparib in patients with solid tumors; this portion identified 600 mg BID as the recommended starting dose for future studies (n = 56; completed).
  - Part 2: a Phase 2 portion evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a BRCA mutation.
    - Part 2A enrolled patients with a gBRCA mutation who had received 2 to 4 prior treatment regimens (n = 42; enrollment complete).
    - Part 2B enrolled patients with a gBRCA or sBRCA mutation who received at least 3 prior chemotherapy regimens (n = 12; enrollment complete).
    - Part 3: a Phase 2 portion in patients with a relapsed solid tumor associated with a BRCA mutation in order to characterize the PK, food effect, and safety profile of a higher dose strength tablet (n = 26; enrollment complete).
- CO-338-045 (ADME study): a Phase 1 mass balance study of [^{14}C]-rucaparib in patients with an advanced solid tumor (n = 6; completed).

Ongoing Studies

- CO-338-017 (ARIEL2): a 2-part open-label Phase 2 study of monotherapy oral rucaparib for treatment of relapsed, high-grade ovarian cancer patients. It is designed to identify tumor characteristics that may predict sensitivity to rucaparib. Patients will be classified into molecularly-defined subgroups, including tumor BRCA (tBRCA, inclusive of both germline and somatic BRCA) and BRCA-like, by a prospectively defined genomic signature.
  - Part 1 enrolled patients with platinum-sensitive, relapsed disease who received ≥ 1 prior platinum regimen (n = 204; enrollment complete).
  - Part 2 enrolled patients with relapsed disease who received at least 3 prior chemotherapy regimens (n = 287; enrollment complete).

- CO-338-014 (ARIEL3): a Phase 3, randomized, double-blind study of monotherapy oral rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy (n = 564 [randomized patients; rucaparib n = 375; placebo n = 189]; enrollment complete).
- CO-338-043 (ARIEL4): a Phase 3, randomized study of rucaparib versus chemotherapy in patients with relapse, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (n = 345 planned).
- CO-338-044 (DDI study): a 2-part, Phase 1, open-label, multiple-probe drug-drug interaction (DDI) study to determine the effect of rucaparib on PK of caffeine, S-warfarin, omeprazole, midazolam, and digoxin in patients with advanced solid tumors in Part 1, followed by optional continued treatment with rucaparib in Part 2 (n = 17; enrollment complete).
- CO-338-063 (TRITON3): a Phase 3 study evaluating monotherapy rucaparib versus physician's choice of therapy (abiraterone acetate, enzalutamide, or docetaxel) for the treatment of mCRPC patients with a BRCA1/2 or ATM mutation who have received prior treatment with AR-directed therapy, but have not yet received taxane chemotherapy in the castration resistant setting (n = 400 planned; enrollment ongoing).
- CO-338-078 (hepatic impairment study): a Phase 1, clinical pharmacology study in patients with an advanced solid tumor and normal or moderately impaired hepatic function to assess the effect of hepatic function on rucaparib PK.

3.4.2.1 Overview of Pharmacokinetics and Drug-Drug Interactions

An overview of data are provided below and described in detail in the rucaparib IB.

Assessment of rucaparib PK in cancer patients showed an approximate dose proportional exposure after QD or BID dosing, rapid absorption with C_{max} achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and elimination ranged from 11 to 29.8 hours. Rucaparib was moderately bound to human plasma proteins *in vitro*.

At a dose of 600 mg BID rucaparib, steady state was achieved after approximately 1 week. The absolute oral bioavailability was 37.2%. In the presence of a high-fat meal, there was a slight delay in absorption, but an overall increase in exposure and oral bioavailability (51.7% [fed] vs. 36.2% [fasted]).

In vitro, CYP enzymes were shown to contribute to rucaparib metabolism. In a preliminary assessment of rucaparib metabolism in patients, rucaparib biotransformation pathways included hydroxylation or oxidation, N-demethylation, deamination, and phase II methylation. A carboxylic acid metabolite (M324) and a phase II N-methylated metabolite of M324 (M338) were identified as major metabolites.

POPULATION PK ANALYSES

Drug interactions with rucaparib as a substrate were assessed in a population PK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyperinducers) did

not significantly impact the steady-state exposure of rucaparib at 600 mg twice daily. Concomitant administration of strong CYP1A2 or CYP2D6 inhibitors did not significantly impact rucaparib PK. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play limited role in rucaparib metabolism *in vivo*, and no rucaparib dose adjustment is needed when concomitantly administered with CYP1A2 or CYP2D6 inhibitors.

Concomitant treatment with PPIs did not show clinically significant effect on rucaparib PK. No dose modification is recommended based on use of PPIs.

EFFECT OF RUCAPARIB ON THE PHARMACOKINETICS OF OTHER DRUGS

In the "cocktail" drug-drug interaction study CO-338-044, the effects of steady-state rucaparib at 600 mg twice daily on CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp were evaluated with single oral doses of sensitive probes (caffeine, S-warfarin, omeprazole, midazolam, and digoxin, respectively). Data suggest that rucaparib is a moderate inhibitor of CYP1A2, a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibited P-gp in the gut but the effect is unlikely clinically significant. Details and results of study CO-338-044 are provided in the rucaparib IB.

3.4.2.2 Overview of Efficacy

An overview of data are provided below and described in detail in the rucaparib IB.

Efficacy analysis was based on pooled efficacy data from 106 patients with BRCA mutant ovarian cancer, who received 2 or more prior chemotherapy regimens, and who initiated treatment with rucaparib at 600 mg BID in Part 2A of Study CO-338-010 and Parts 1 and 2 of Study CO-338-017. The enrollment cut-off date was 1 October 2015 (all 42 patients enrolled) and the visit data cut-off date was 30 November 2015 for Study CO-338-010 Part 2A. The enrollment cut-off was a 1 October 2015 and the visit data cut-off was 29 February 2016 for Part 1 (24 patients) and Part 2 (40 patients) of Study CO-338-017.

Efficacy data indicate that many patients with advanced ovarian cancer associated with a BRCA1/2 mutation and who had 2 or more prior therapies achieve RECIST and/or GCIG CA-125 responses. The confirmed ORR per RECIST by investigator review was 53.8% (57/106) and the confirmed response by RECIST or GCIC-CA-125 was 70.8% (75/106). The confirmed ORR per RECIST by independent review was 41.5% (44/106).

In addition, patients without a BRCA1/2 mutation in tumor tissue are also deriving benefit, with 43% achieving RECIST and/or GCIG CA-125 responses.

In the Phase 3, randomized, double-blind study of monotherapy oral rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy (ARIEL3), the primary efficacy endpoint was investigator-assessed PFS (invPFS) by RECIST v1.1. Three patient populations (tBRCA, HRD, and intent-to-treat [ITT]) were evaluated in a step-down analysis.

The primary endpoint was achieved as of 15 April 2017 with a highly statistically significant difference in invPFS between rucaparib treatment as compared to placebo for each of the 3 stratified primary efficacy analysis populations ($p < 0.0001$ for each population). The median invPFS in the tBRCA population was 16.6 months (95% CI, 13.4-22.9) for the rucaparib group and 5.4 months (95% CI, 3.4-6.7) for the placebo group. Additional data in HRD and ITT populations are available in the rucaparib IB.

For each of the 3 populations, the confirmed investigator-assessed ORR, per RECIST v1.1, in patients with measurable disease at baseline was statistically significantly higher in the rucaparib group compared to the placebo group. In the tBRCA population, the confirmed ORR was 15/40 (37.5%) for the rucaparib group and 2/23 (8.7%) for the placebo group ($p = 0.0055$). Additional data in HRD and ITT populations are available in the rucaparib IB.

Four mCRPC patients, who were tested BRCA mutation positive and had progressive disease, received rucaparib monotherapy in Study CO-338-010 with rucaparib or under named patient access. Information is available for 3 patients, all of whom experienced tumor stabilization, decrease of PSA levels, and/or symptom improvement.

3.4.2.3 Overview of Safety

An overview of data are provided below and described in detail in the rucaparib IB.

Integrated Safety Analysis in the Treatment Setting (Studies CO-338-010 and CO-338-017)

An integrated safety analysis, based on pooled safety data from 545 patients in Study CO-338-010 (Parts 2A and 2B) and Study CO-338-017 (ARIEL2; Parts 1 and 2) with relapsed ovarian cancer who were treated with 600 mg BID monotherapy rucaparib, was performed and a summary of TEAEs, overall and ≥ Grade 3, is presented in Table 1. This analysis includes data as of 1 September 2017. Overall, the median duration of treatment was 160.0 days (approximately 5.3 months; range, 2 to 1234 days).

The most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and included gastrointestinal disorders (nausea [78.5%], vomiting [45.9%], constipation [37.6], abdominal pain (32.5%), and diarrhea [32.3%]), asthenia/fatigue (75.0%), anemia/decreased haemoglobin (44.0%), ALT/AST increased (39.3%), decreased appetite (38.3%), and dysgeusia (36.7%).

The most common treatment-related TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and included nausea (68.3), asthenia/fatigue (67.0%), anemia/decreased haemoglobin (38.9%), ALT/AST increased (36.5%), dysgeusia (34.1%), and vomiting (31.6%) as described in greater detail in the rucaparib IB.

The most common TEAEs ≥ Grade 3 were anemia/decreased hemoglobin (24.2%), asthenia/fatigue (11.7%), ALT/AST increased (10.8%), thrombocytopenia/decreased platelets (6.1%), and nausea (5.3%). As of the data cut-off date, approximately 9% of patients had discontinued due to a treatment-related TEAE.

In addition, photosensitivity has been reported in some patients. Photosensitivity was initially reported in the Phase 1 dose-escalation portion of Study CO-338-010 (n=6; 10.7%) and based on these reports of photosensitivity, guidance for sun protection was included in rucaparib clinical studies. Of 917 patients with advanced ovarian cancer treated with rucaparib 600 mg BID in Studies CO-338-014 (ARIEL3), CO-338-010, and CO-338-017 (ARIEL2), 118 patients (12.9%) experienced photosensitivity, of whom 2 patients (0.2%) experienced ≥ Grade 3 photosensitivity as described in the rucaparib IB. Patients should use typical precautions when going outside, such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

Effects on cardiac channel activity *in vitro* and a comprehensive assessment of the effects of rucaparib on ECG parameters in cancer patients demonstrated a low risk of cardiac effects by rucaparib.

Table 1. Treatment-emergent AEs (All Grades and ≥ Grade 3) Reported in ≥ 20% of Ovarian Cancer Patients in Combined Studies CO-338-010 and CO-338-017

Preferred Term[a]	600 mg BID Rucaparib (N = 545)[b] n (%)	
	All Grades	≥ Grade 3
Nausea	428 (78.5)	29 (5.3)
Asthenia/fatigue[c]	409 (75.0)	64 (11.7)
Vomiting	250 (45.9)	23 (4.2)
Anemia/decreased hemoglobin[c]	240 (44.0)	132 (24.2)
ALT/AST increased[c]	214 (39.3)	59 (10.8)
Decreased appetite	209 (38.3)	16 (2.9)
Constipation	205 (37.6)	8 (1.5)
Dysgeusia	200 (36.7)	1 (0.2)
Abdominal pain	177 (32.5)	22 (4.0)
Diarrhoea	176 (32.3)	11 (2.0)
Thrombocytopenia/decreased platelets[c]	128 (23.5)	33 (6.1)
Blood creatinine increased	120 (22.0)	3 (0.6)
Dypsnoea	120 (22.0)	5 (0.9)

Note: Data are presented by decreasing frequency for TEAEs of all grades, all causality.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST – aspartate aminotransferase; BID = twice a day; MedDRA = Medical Dictionary for Regulatory Activities; N or n = number of patients; TEAE = treatment-emergent adverse event.

[a] Preferred Terms were based on MedDRA dictionary (version 18.1);

[b] The data presented in this table are from: all ovarian cancer patients treated with rucaparib 600 mg BID and enrolled in Parts 2A and 2B of Study CO-338-010 and Parts 1 and 2 of Study CO-338-017, with a data cut-off date of 1 September 2017.

[c] Combined MedDRA preferred terms

Safety in the Maintenance Setting (Study CO-338-014 [ARIEL3])

As of the 15 April 2017 cut-off date for Study CO-338-014 (ARIEL3), a total of 561 patients were treated with at least 1 dose of study drug (372 patients in the rucaparib group and 189 patients in the placebo group). The median duration of treatment was 8.3 months (range: 0-35) in the rucaparib group and 5.5 months (range, 0 to 35) in the placebo group.

The TEAEs that occurred in ≥ 20% of patients (all grades) in either treatment group are summarized by PT in Table 2. The most common TEAEs that occurred in the rucaparib group were nausea (75.3%), asthenia/fatigue (69.4%), dysgeusia (39.2%), and anemia/low or decreased hemoglobin (37.4%). Although greater incidences of these most common TEAEs occurred with rucaparib treatment compared to placebo, the TEAEs reported for the placebo group provide a general context of what events are prevalent in this patient population without treatment. The most common TEAEs that reported in the placebo group were nausea (36.5%), asthenia/fatigue (43.9%), abdominal pain (25.9%), and constipation (23.8%).

Grade 3 or higher TEAEs are also summarized in Table 2. Approximately half (56.2%) of the patients treated with rucaparib experienced a TEAE of Grade 3 or higher compared to approximately 15% of placebo patients. For patients in the rucaparib group, 2 TEAEs that were Grade 3 or higher had an incidence of > 10%: anemia/low or decreased hemoglobin (18.8%) and increased ALT/AST (10.5%). No Grade 4 events of increased ALT/AST were reported.

Table 2. Treatment-emergent AEs Reported in ≥ 20% of Patients (All Grades) in Any Treatment Group in Study CO-338-014 - Safety Population

Preferred Term(s)	All Grades		≥ Grade 3[a]	
	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)	Rucaparib (N = 372) n (%)	Placebo (N = 189) n (%)
Number of Patients With at Least One TEAE	**372 (100)**	**182 (96.3)**	**209 (56.2)**	**28 (14.8)**
Nausea	280 (75.3)	69 (36.5)	14 (3.8)	1 (0.5)
Asthenia/Fatigue	258 (69.4)	83 (43.9)	25 (6.7)	5 (2.6)
Dysgeusia	146 (39.2)	13 (6.9)	0	0
Anemia and/or low/decreased hemoglobin	139 (37.4)	11 (5.8)	70 (18.8)	1 (0.5)
Constipation	136 (36.6)	45 (23.8)	7 (1.9)	2 (1.1)
Vomiting	136 (36.6)	28 (14.8)	15 (4.0)	2 (1.1)
ALT/AST Increased	126 (33.9)	7 (3.7)	39 (10.5)	0
Diarrhea	118 (31.7)	41 (21.7)	2 (0.5)	2 (1.1)
Abdominal pain	111 (29.8)	49 (25.9)	9 (2.4)	1 (0.5)
Thrombocytopenia and/or low/decreased platelets	104 (28.0)	5 (2.6)	19 (5.1)	0
Decreased appetite	87 (23.4)	26 (13.8)	2 (0.5)	0

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event.

[a] NCI CTCAE grade.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin, increased ALT, increased AST, and increased serum creatinine, most common (Table 3).

Decreased platelets, neutrophils, lymphocytes, and increased cholesterol were observed to a lesser extent (Table 3).

A decrease in hemoglobin (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1-4) from baseline was observed in 61% of patients (Grade 3, 13%). A decrease in lymphocytes, platelets, or neutrophils from baseline to a worsening CTCAE Grade occurred in 24%, 40%, and 35% of all patients, respectively). A shift to CTCAE Grade 3 or greater lymphocytes, platelets, or neutrophils was observed in 5%, 2%, and 6%, of all patients, respectively.

Notable shifts from baseline were observed for creatinine, ALT, AST, and cholesterol concentrations in the majority of patients. An increase in ALT or AST from baseline to a worsening CTCAE grade was observed in 73% and 61% of patients, respectively. A shift to CTCAE Grade 3 or greater ALT or AST was observed in 7% and 1% of all patients, respectively.

Increases in ALT/AST are a known self-limiting effect of rucaparib treatment; therefore, management of these elevations was specified within the protocol. Elevations in ALT/AST were generally not accompanied by a concomitant elevation in bilirubin outside the normal range, and no cases met Hy's Law criteria for drug-induced liver injury. Continued dosing with rucaparib in the presence of Grade 3 ALT/AST elevations is permitted if there are no other signs of liver toxicity.

An increase in serum creatinine from baseline to a worsening CTCAE Grade occurred in 43% of patients (0.3% Grade 3) using an updated version of the CTCAE (ie, version 5). In CTCAE version 4.03, any increase in creatinine above the baseline value is assessed as a Grade 1 toxicity (1 to 1.5 x baseline value) and almost all patients exhibit a shift from baseline creatinine. In CTCAE version 5, Grade 1 for increased creatinine is based on values greater than the upper limit of normal (ULN). The elevations were observed early in treatment (Day 15 of Cycle 1) and then stabilized with continued rucaparib treatment. Serum creatinine levels decreased with interruption or discontinuation of rucaparib, and increase again with resumption of treatment.

An increase in total cholesterol from baseline to a worsening CTCAE Grade occurred in 41% of all patients (4% Grade $\geq$ 3).

Overall, rucaparib safety data at a dose of 600 mg BID in patients with ovarian cancer in Study CO-338-014 in the maintenance setting were consistent with the combined safety data in patients with ovarian cancer from Studies CO-338-010 and CO-338-017 in the treatment setting.

Table 3. Change from Baseline in Laboratory Parameters in Patients Treated with 600 mg BID Rucaparib (Study CO-338-014)

	Rucaparib (N=372)		Placebo (N=189)	
Shift in CTCAE Grade (n [%])[a]				
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Decrease in hemoglobin[b]	224 (61.0)	46 (12.5)	24 (12.7)	2 (1.1)
Decrease in lymphocytes[b, c]	87 (23.7)	17 (4.6)	31 (16.5)	5 (2.7)
Decrease in neutrophils[b, c]	128 (34.9)	23 (6.3)	32 (17.0)	4 (2.1)
Decrease in platelets[b]	145 (39.5)	8 (2.2)	15 (8.0)	0
Shift in CTCAE Grade (n [%])[a]				
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Increase in ALT[b]	267 (72.8)	24 (6.5)	7 (3.7)	0
Increase in AST[c, d]	223 (60.9)	3 (0.8)	7 (3.7)	0
Increase in alkaline phosphatase[b]	116 (31.6)	1 (0.3)	10 (5.3)	0
Increase in bilirubin[b]	34 (9.3)	1 (0.3)	3 (1.6)	0
Increase in cholesterol[b]	152 (41.4)	15 (4.1)	39 (20.6)	0
Hyperglycemia[b]	125 (34.1)	6 (1.6)	54 (28.6)	0
Increase in creatinine[b, e]	156 (42.5)	1 (0.3)	14 (7.4)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice a day; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

[a] Shifts are based on worst grade experienced on treatment and patients who had at least a 1 grade shift from baseline.

[b] rucaparib n = 367

[c] placebo n = 188

[d] rucaparib n = 366

[e] Evaluated using CTCAE, v5 where Grade 1 is >ULN-1.5 ULN; Grade 2 is >1.5 x baseline to 3.0 x baseline or >1.5 x ULN to 3.0 x ULN; Grade 3 is >3.0 x baseline or >3.0 x ULN to 6.0 x ULN; and Grade 4 is >6.0 x ULN.

Adverse Events of Special Interest

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESI), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, and in some cases a deleterious BRCA mutation, which increases the risk of developing cancer(s). Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. More information on

AESIs of MDS/AML experienced by patients in rucaparib clinical studies is provided in the rucaparib IB.

Adverse events (AEs) of pneumonitis have been reported with PARP inhibitor treatment, including in clinical trials evaluating rucaparib. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment, and causality assessment is often confounded by lack of a consistent clinical pattern as well as other pre-disposing factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. Clovis is seeking to understand whether or not there is a relationship between pneumonitis and rucaparib treatment; thus, Clovis is designating pneumonitis as an AESI to gather data to enable a thorough evaluation and assessment of the event and associated terms specified in Section 10.7. Also, refer to the rucaparib IB for information regarding the AESI of pneumonitis.

3.5 Rationale for this Study of Rucaparib

Homologous recombination deficiency has been observed in many carcinomas, including prostate cancer. Men with a germline mutation in BRCA2 are at increased risk for developing prostate cancer, estimated at 2.5 to 8.6-fold compared with non-carriers.[6] Men with prostate cancer and a germline mutation in BRCA2 typically develop disease at a younger age, have more aggressive features and higher mortality rates; while less common in prostate cancer, germline mutations in BRCA1 are also associated with more aggressive disease.[7] Deleterious germline mutations in other HRR genes, including ATM, CHEK2, RAD51D and PALB2,[30] have also been reported. In addition to germline mutations, somatic mutations in the HRR genes ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51B, and RAD51C have been observed in advanced prostate cancer.[8, 9]

Nonclinical evaluation has demonstrated sensitivity of BRCA1 and BRCA2 homozygous mutant cell lines to rucaparib and other PARP inhibitors (see Section 4.1 of the Investigator's Brochure). In addition, sensitivity to PARP inhibition has also been observed in cells deficient or depleted in other components of HRR, such as RAD51, RAD54L, ATM, CHEK2, NBN, or FANCA.[31] This sensitivity is the result of synthetic lethality in homologous recombination deficient cells (like BRCA mutant tumors) when exposed to a PARP inhibitor.

Rucaparib, olaparib, niraparib, and talazoparib, similar agents in the growing class of PARP inhibitors in clinical development, have demonstrated clinical activity in several trials as a single agent for treatment of ovarian, prostate, and breast cancer associated with a BRCA mutation (germline or somatic), as well as in patients without a BRCA mutation.[9, 32-40]

The response to PARP inhibitors in mCRPC patients has been explored in several Phase 1 studies. Fong et al. provided the first description of a BRCA mutant prostate cancer patient responding to PARPi therapy.[41] In a Phase 1 dose-escalation trial of olaparib, 3 mCRPC patients were enrolled, of which 1 patient was a germline BRCA2 mutation carrier. This BRCA mutant mCRPC patient had a > 50% reduction in his PSA level, resolution of bone metastases, and treatment duration > 1 year. The 2 mCRPC patients without a germline BRCA mutation did not demonstrate a similar response.

Sandhu et al. reported on a cohort of 4 patients with germline BRCA2-mutant advanced prostate cancer treated with either olaparib (3 patients) or niraparib (1 patient).[42] In the patients treated with olaparib, PSA and radiological responses lasting 34 and 26 months were noted in 2 patients, and SD of 10 months was noted in the 3rd. The patient treated with niraparib demonstrated primary resistance and quickly progressed; the total duration for niraparib treatment in that patient was 6 weeks.

Olaparib was further evaluated in mCRPC in several Phase 2 studies. In one trial that enrolled multiple tumor types, Kaufman et al. (2014) reported efficacy data for 8 BRCA mutant mCRPC patients who had received a median number of 2 prior therapies.[43] All patients had experienced disease progression following hormonal therapy; 75% had received prior docetaxel, and 50% had received prior platinum (carboplatin or cisplatin). Four patients had a confirmed PR (confirmed RECIST ORR=50%) and 2 patients (25%) had a best response of SD. Overall duration of response was 327 days, PFS was 7.2 months and median OS was 18.4 months.

More recently, olaparib demonstrated compelling clinical activity in a Phase 2 open-label investigator-sponsored study[9] evaluating mCRPC patients with evidence of HRD. In the Trial of PARP Inhibition in Prostate Cancer (TOPARP) study, which enrolled 50 mCRPC patients who received prior docetaxel (100%), abiraterone or enzalutamide (98%), and cabazitaxel (58%), olaparib demonstrated an ORR of 33% in 49 evaluable patients. Response was defined as any of the following: response according to RECIST version 1.1; at least 50% reduction in PSA level; or a confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL. The ORR in patients with a mutation in a DNA repair gene (n = 16) was 88%, including 7/7 patients with a BRCA2 mutation and 4/5 patients with an ATM mutation. Median rPFS and OS in patients classified as biomarker positive (with HRR gene mutation) were 9.8 months and 13.8 months, respectively, compared to 2.7 months and 7.5 months for patient classified as biomarker negative (no HRR gene mutation).

To date, rucaparib has exhibited clinical activity and an acceptable safety profile when administered as monotherapy. Details of the rucaparib clinical studies and efficacy data are further described in Section 3.4.2 and Section 3.4.2.2, as well an in the IB (Sections 5.1 and 5.3). Complete and partial responses, as defined by RECIST criteria, as well as durable stable disease, have been observed in patients with ovarian, breast and pancreatic cancer treated with monotherapy rucaparib. Robust efficacy has been observed in ovarian cancer patients with a BRCA mutation (germline and somatic) (Section 3.4.2.2) and in patients who have a BRCA-like tumor (ie, did not have a BRCA mutation, but had a high percentage of tumor genome loss of heterozygosity [LOH]), including patients with a deleterious mutations in RAD51C or RAD51D. Four mCRPC patients, who were tested BRCA mutation positive and had progressive disease, received rucaparib monotherapy in Study CO-338-010 with rucaparib or under named patient access and experienced tumor reduction, decrease of PSA levels, and symptom improvement. Rucaparib monotherapy is well tolerated by patients and has a well-established and manageable safety profile.

Taken together, nonclinical and clinical data with rucaparib and other PARP inhibitors provide a compelling evidence for use of rucaparib in a selected population of CRPC patients with predicted loss-of-function mutations in HRR genes such as BRCA1/2 and ATM, as well as in HRR genes such as BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51,

RAD51B, RAD51C, RAD51D, or RAD54L, where deleterious mutations have generally been observed at lower frequencies.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

- To assess the efficacy of rucaparib based on the response rate in mCRPC patients with HRD who progressed on AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) and taxane-based chemotherapy in the castration-resistant setting

4.2 Secondary Objectives

The secondary objectives of this study are:

- To assess duration of response (DOR)
- To assess radiologic PFS (rPFS)
- To assess OS
- To assess clinical benefit rate (CBR)
- To assess PSA response ≥ 50% (all patients)
- To assess PSA response ≥ 90% (all patients)
- To assess time to PSA progression
- To characterize the steady-state pharmacokinetics of rucaparib in mCRPC patients
- To assess safety and tolerability

4.3 Exploratory Objectives

Exploratory objectives in this study are:

- To evaluate patient reported outcomes (PRO) using the EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L), Functional Assessment of Cancer Therapy-Prostate (FACT-P), analgesic drug score, and Brief Pain Inventory – Short Form (BPI-SF) instruments
- To assess changes in the molecular profile over time of matched pre- and post-treatment tumor or plasma samples
- To assess concordance in HRR gene mutation status in matched Pre-Screening biopsy tissue, archival primary and metastatic tumor tissue, and plasma circulating tumor DNA (ctDNA)
- To assess ctDNA as a molecular marker of response

- To assess time to first subsequent antineoplastic therapy
- To evaluate loss of heterozygosity (LOH) in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples
- To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This is a Phase 2 multicenter study evaluating rucaparib for treatment of patients with mCRPC whose tumors are associated with HRD. This study will enroll mCRPC patients with deleterious mutations in BRCA1/2, ATM , or other HRR genes associated with sensitivity to PARPi (Appendix 1). Deleterious mutations are defined as protein-truncating mutations, large protein-truncating rearrangements, splice site mutations, deleterious missense mutations, and homozygous deletions. Mutations may be identified by local testing, or through central testing provided by the sponsor during Pre-Screening. For local test results, the classification of the mutation as deleterious must be documented in the patient's medical record.

All patients will be required to have progressed on prior AR-targeted therapy (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent) after receiving treatment with at least 1, but no more than 2, of these agents. Patients must also have progressed after 1 prior line of taxane-based chemotherapy for mCRPC. Patients who received prior PARPi treatment, mitoxantrone, cyclophosphamide or platinum-based chemotherapy will be excluded.

This study consists of a Pre-Screening Phase (Section 5.1.1), Screening Phase (Section 5.1.2), Treatment Phase (Section 5.1.3), and Post-Treatment Phase (Section 5.1.4). Patients will receive rucaparib monotherapy in the Treatment Phase, and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study.

5.1.1 Pre-Screening Phase

The Pre-Screening Phase is to identify eligible deleterious HRR gene mutations through central testing of tumor tissue and plasma. Patients who have an eligible deleterious HRR gene mutation identified through local testing need not enter Pre-Screening and the patient should proceed to the Screening Phase.

To enter Pre-Screening, patients should have evidence of radiographic or biochemical disease progression, and be eligible for this study as their immediate next therapy. Patient tissue and plasma samples should be submitted simultaneously during Pre-Screening. Tissue submitted for Pre-Screening testing should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy and the patient consents to this procedure. If a metastatic biopsy is not feasible, archival tissue samples should be submitted. To reduce the chance of test failure, archival tissue should be < 3 years old. If plasma or tissue samples result in test failure, sites are encouraged to submit additional samples, as available, in order to obtain a successful test result. Patients who have an eligible deleterious HRR gene mutation identified during Pre-Screening may proceed to the Screening Phase. A study schema for the Pre-Screening Phase is provided in Figure 1.

In the event that a deleterious BRCA1/2, ATM, or other HRR gene mutation is identified in plasma or tumor tissue during the Pre-Screening Phase, the patient may be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If

the patient chooses to have germline testing performed, this result will be entered in the clinical trial database for this study.

During the Pre-Screening Phase, unless otherwise required by local regulations, SAEs which are related to protocol-mandated assessments will be reported.

5.1.2 Screening Phase

After providing consent to participate, patients with a deleterious BRCA1/2, ATM, or other HRR gene mutation will undergo Screening assessments within 28 days prior to the first dose of rucaparib. Patients will undergo procedures and assessments during Screening Phase as described in Section 9.4.

During the Screening Phase, unless otherwise required by local regulations, serious adverse events (SAEs) which are related to protocol-mandated assessments will be reported.

Additional screening assessments will include collection of the patient's medical information and demographics, physical exam, laboratory safety assessments, tumor assessments, PRO instruments, and blood and tissue samples to support exploratory objectives as described in Section 9.4.

Enrollment will require prospective sponsor (or designee) review and confirmation of eligibility, including, but not limited to:

- BRCA/ATM/other HRR gene test result by either local or central testing
- details of prior therapy for prostate cancer
- screening laboratory assessments

5.1.3 Treatment Phase

Rucaparib will be administered at a starting dose of 600 mg BID. During the Treatment Phase, patients will undergo procedures and assessments including regular evaluations for safety and efficacy as described in Section 9.5.

Tumor assessments by CT/MRI and bone scans will be performed during screening, at the end of every 8 calendar weeks (± 7 days) from Study Day 1 (Week 1) up to 24 weeks and every 12 calendar weeks (± 7 days) thereafter, and at the Treatment Discontinuation Visit, if applicable. Modified RECIST Version 1.1 criteria will be used to document radiologic response in soft tissue (visceral and nodal) disease and PCWG3 criteria will be used to document radiologic progression in bone lesions. If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented. Any drug modifications (interruption, dose reduction, or discontinuation) should be documented in the eCRF and source documents. If study treatment is interrupted, tumor assessments will not be delayed and will be performed on the regular study schedule. Copies of all radiologic scans will be collected for central independent radiology review (IRR).

Patients will receive rucaparib until confirmed radiologic disease progression assessed by investigator based on modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up; or withdrawal of consent. PSA rise without evidence of confirmed radiologic progression is strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy and is discouraged as a criterion to start a new systemic antineoplastic therapy throughout the study. Palliative radiation for treatment of painful bony metastases and initiation of bisphosphonates or other approved bone-targeting agents are allowed and should not result in discontinuation of study drug therapy. Patients who discontinue study treatment for reasons other than radiologic disease progression, should continue radiologic tumor assessment performed as described in Section 5.1.4.

If a patient has radiologic progression, but continues to derive clinical benefit per the investigator, then continuation of treatment beyond progression may be requested by the investigator as per Section 7.4.4. In such cases, the decision to continue will be made jointly between the investigator and the sponsor (or designee), and the patient must consent prior to continuing treatment with rucaparib. These patients will continue to undergo all protocol required assessments specified in Table 5.

Patient safety will be monitored on a regular basis using procedures and assessments described in Section 9 and Section 13.4. Safety data will be periodically reviewed by the Data Monitoring Committee (DMC) as described in Section 13.6. The DMC will comprise study investigators and sponsor representatives. The DMC will meet after the first 20 patients received rucaparib for at least 28 days or discontinued study treatment, and then at least semi-annually after sufficient data has been collected.

5.1.4 Post-treatment Phase

The sponsor (or designee) should be notified of all treatment terminations as soon as possible. The date and reason for cessation of study drug must be documented in the eCRF and source documents. Patients will undergo procedures and assessments during the Post-treatment Phase as described in Section 9.6. Upon treatment discontinuation, patients will have a Treatment Discontinuation Visit (Section 9.6.1), a 28-Day Follow-up Visit (Section 9.6.2), and then will proceed to long-term follow-up (Section 9.6.3). An optional tumor biopsy will be collected prior to the start of subsequent anticancer therapy from patients who experience radiographic or unequivocal clinical disease progression and who provide appropriate consent. For patients who had their last tumor assessment ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) prior to Treatment Discontinuation Visit, a tumor assessment must be performed.

If treatment was discontinued for reasons other than radiologic disease progression, radiologic tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) and PRO assessments will continue until confirmed radiographic disease progression. For these patients, tumor assessments should continue to be performed at the end of every 8 calendar weeks (±7 days) relative to Study Day 1 (Week 1) up to 24 weeks and then every 12 calendar weeks (±7 days) thereafter, until confirmed radiologic disease progression by modified RECIST Version 1.1 and PCWG3 (for bone lesions only) criteria as assessed by the investigator, loss to follow-up, withdrawal of consent, or study closure. For patients who start subsequent

anticancer therapy, tumor assessments will continue until radiologic disease progression is confirmed.

Ongoing SAEs, AESIs, and treatment related Grade 3/4 AEs will be followed until either resolution or stabilization has been determined or until loss to follow-up. After the 28-Day Follow-up Visit, only SAEs considered as potentially related to study drug should be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the 28-Day Follow-up Visit (28-days after the last dose of rucaparib).

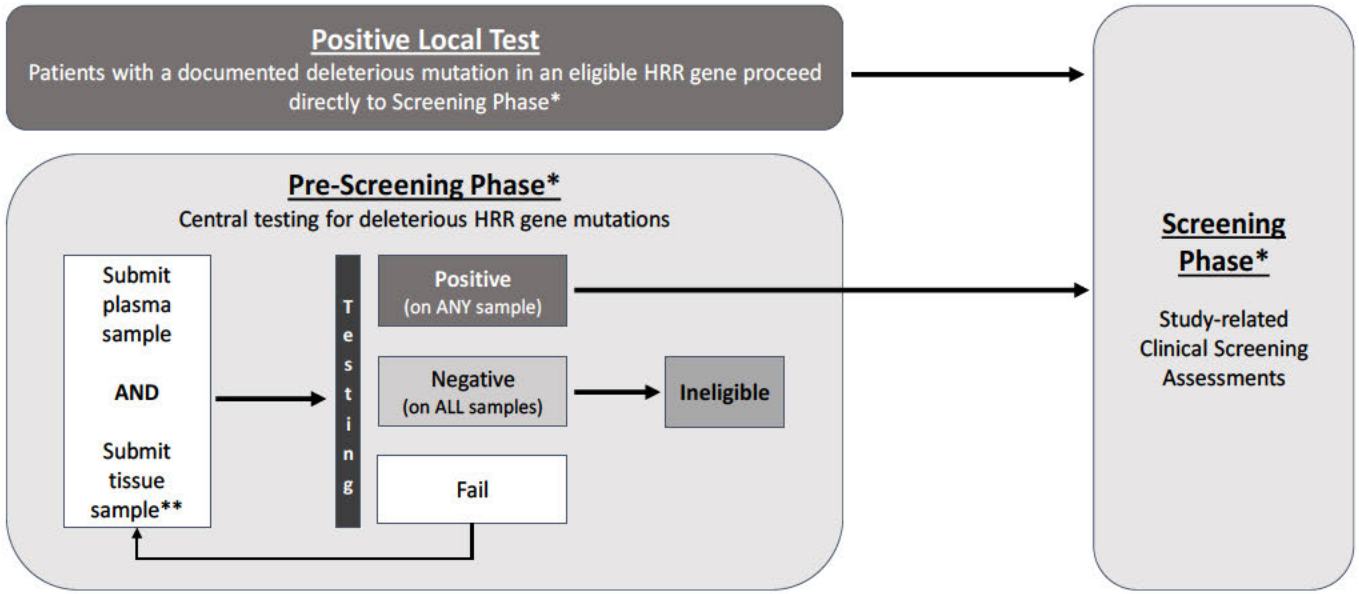
All patients will be followed for survival and subsequent treatments every 12 weeks (± 14 days) relative to the last dose of rucaparib until death, loss to follow-up, withdrawal of consent, or study closure.

5.2 Study Schema

The Pre-Screening Phase study schema is provided in Figure 1.

The study schema for Screening, Treatment, and Post-treatment Phases is provided in Figure 2.

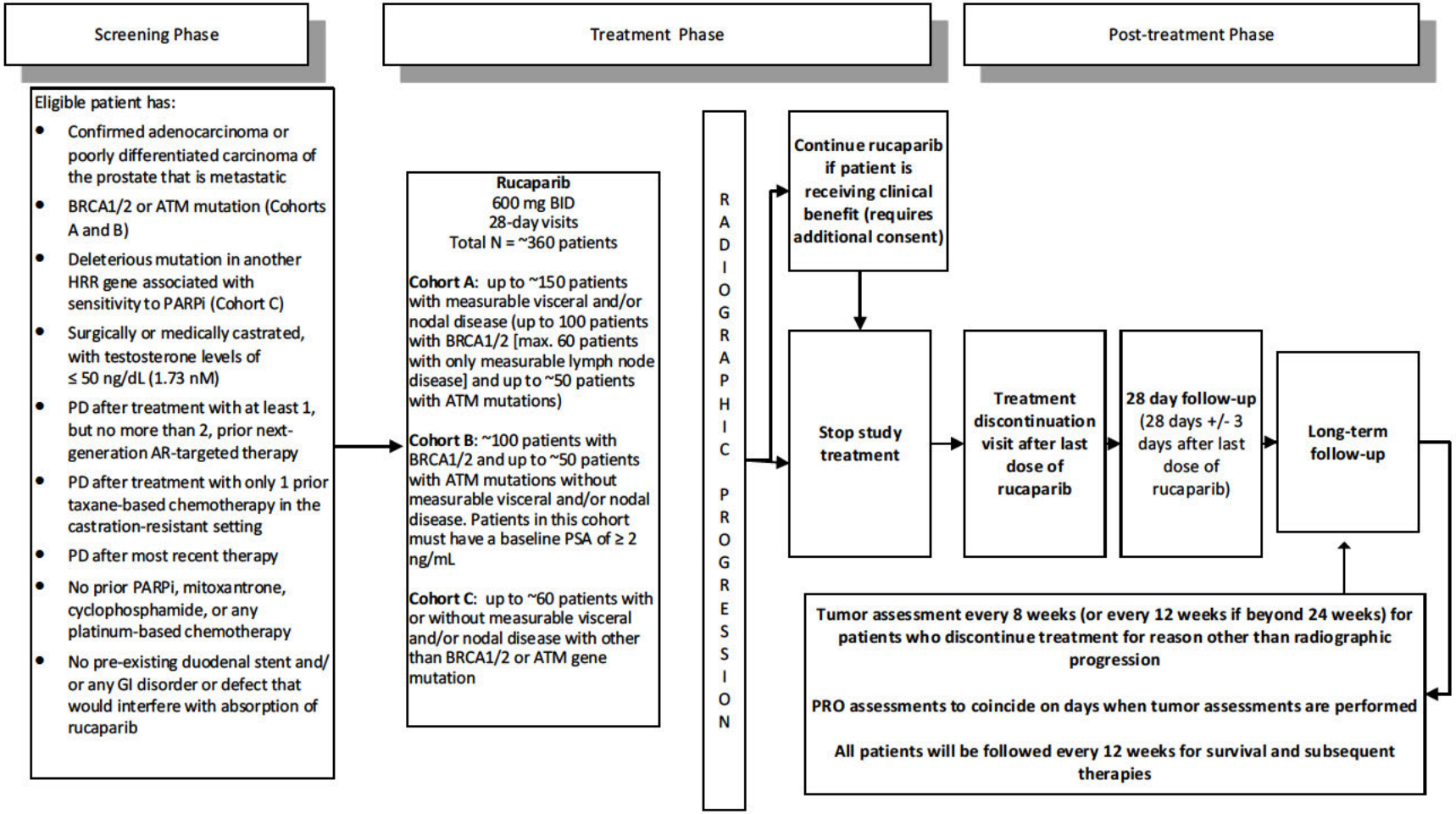
Figure 1. Pre-Screening Study Schema



* Patients should be demonstrating radiographic or biochemical progression in order to enter the Pre-Screening and Screening Phases

** Metastatic biopsy (preferred) or archival tissue; tissue samples should be < 3 years old

Figure 2. Study Schema: Screening, Treatment, and Post-treatment Phases



5.3 End of Study

The study will close when all enrolled patients have discontinued treatment and completed the 28-Day Follow-up visit. Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of entering an extension protocol in which they can continue to receive rucaparib.

The sponsor may discontinue the study early for any reason as noted in Section 13.7.

6 STUDY POPULATION SELECTION

6.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 360 patients.

Cohort A will include up to 100 patients with a deleterious BRCA1/2 mutation who have measurable visceral and/or nodal disease (with a maximum of 60 patients who have only measurable lymph node disease), and up to approximately 50 patients with a deleterious ATM mutation who have measurable visceral and/or nodal disease.

Cohort B will include up to approximately 100 patients with a deleterious BRCA1/2 mutation and up to approximately 50 patients with a deleterious ATM mutation who do not have measurable visceral and/or nodal disease. Patients in this cohort must have a baseline PSA of ≥ 2 ng/mL.

Cohort C will include up to approximately 60 patients with or without measurable visceral and/or nodal disease who have a deleterious mutation in a HRR gene other than BRCA1/2 or ATM (Appendix 1). Patients without measurable disease must have a baseline PSA of ≥ 2 ng/mL.

Patients will be enrolled across approximately 150 sites worldwide.

6.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criteria below apply to all patients.

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee(IEC)-approved informed consent form prior to any study-specific evaluation
2. Male ≥18 years of age at the time the informed consent form is signed
3. Have a histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate (pure small-cell histologies or pure high-grade neuroendocrine histologies are excluded; neuroendocrine differentiation is allowed) that is metastatic
4. Surgically or medically castrated, with serum testosterone levels of ≤ 50 ng/dL (1.73 nM). For patients currently being treated with LHRH analogs (ie, patients who have not undergone an orchiectomy), therapy must be continued throughout the study
5. Evidence of disease progression after prior therapy for prostate cancer:
   a. Disease progression after treatment with at least 1 but not more than 2 prior next generation AR-targeted therapies (abiraterone acetate, enzalutamide, apalutamide, or investigational AR-targeted agent); treatment with the older anti-androgen therapies such as bicalutamide, flutamide, and nilutamide are not counted toward this limit,

      AND

   b. Disease progression after treatment with 1 prior line of taxane-based chemotherapy for castration-resistant disease. Prior taxane therapy administered for hormone-sensitive disease is permitted and is not counted toward this limit
6. Disease progression after initiation of most recent therapy is based on <u>any</u> of the following criteria:

a. Rise in PSA: a minimum of 2 consecutive rising levels, with an interval of ≥ 1 week between each determination. The most recent screening measurement must have been ≥ 2 ng/mL
b. Transaxial imaging: new or progressive soft tissue masses on CT or MRI scans as defined by RECIST 1.1[44]
c. Radionuclide bone scan: at least 2 new metastatic lesions

7. Patients in Cohorts A and B must have a deleterious mutation in BRCA1/2 or ATM
   Patients in Cohort C must have a deleterious mutation in another HRR gene associated with sensitivity to PARPi (Appendix 1)
   Mutations may be identified by local testing, or through central testing by the sponsor of plasma or tumor tissue. For local test results, the classification of the mutation as deleterious must be documented in the patient's medical record
8. Patients in Cohort A must have measurable visceral or nodal disease per RECIST 1.1 criteria (Appendix 2)
   Patients in Cohorts B and C (without measurable disease) must have PSA ≥ 2 ng/mL on the most recent measurement
9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix 3)
10. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to the first dose of rucaparib:
    a. Bone Marrow Function
       i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
       ii. Platelets > 100×10^9/L
       iii. Hemoglobin ≥ 10 g/dL independent of transfusion within 14 days
    b. Hepatic Function
       i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN
       ii. Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
    c. Renal Function
       i. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula (Appendix 4)
11. Male patients who are committed to undertaking the following measures for the duration of the study and after the last dose of rucaparib for the time period specified:
    a. Use a condom during sex while being treated and for 3 months after the last dose of rucaparib,
    b. Do not make semen donations during treatment and for 3 months after the last dose of rucaparib,
    c. Those with female partners of childbearing potential may be enrolled if they are:
       i. Documented to be surgically sterile (ie, vasectomy);
       ii. Committed to practicing true abstinence during treatment and for 3 months after the last rucaparib dose; or
       iii. Committed to using an effective method of contraception (refer to Section 6.4) with their partner during treatment and for 3 months following the last dose of rucaparib
12. Have a life expectancy of at least 6 months

6.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Active second malignancy, with the exception of curatively treated non-melanoma skin cancer, carcinoma *in situ,* or superficial bladder cancer
   a. Patients with a history of malignancy that has been completely treated, and currently with no evidence of that cancer, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant (BMT) > 2 years prior to first dose of rucaparib
2. Prior treatment with any PARP inhibitor, mitoxantrone, cyclophosphamide, or any platinum-based chemotherapy
3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic, previously treated CNS metastases are eligible provided they have been clinically stable (not requiring steroids for at least 4 weeks prior to first dose of rucaparib and have had appropriate scans at screening assessment
4. Symptomatic or impending spinal cord compression unless appropriately treated, clinically stable, and asymptomatic
5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C
7. Received treatment with chemotherapy, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs within < 2 weeks prior to first dose of rucaparib. Treatment with hormonal therapies (with the exception of LHRH analog) must be discontinued at least 7 days prior to the first dose of rucaparib
8. Adverse effect of prior therapy not resolved to CTCAE Grade 1 or below with the exception of alopecia. Ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from the sponsor
9. Initiated low-dose corticosteroid, denosumab, or bisphosphonate therapy or adjusted low-dose corticosteroid, denosumab, or bisphosphonate dose/regimen within < 4 weeks prior to first dose of rucaparib. Patients on a stable low-dose corticosteroid, denosumab, or bisphosphonate regimen are eligible and may continue treatment
10. Non-study related minor surgical procedure within < 5 days, or major surgical procedure within < 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study

6.4 Patients or Partners of Patients Including Those with Reproductive Potential

Male patients are required to use a condom during sex with a partner to avoid the possibility of exposure of the partner to rucaparib.

Male patients must not make semen donations for 3 months after the last dose of rucaparib.

Male patients of reproductive potential must avoid pregnancy in partners who are women of childbearing potential, and such partners should not be considering getting pregnant during the study and for at least 3 months after treatment is discontinued or longer if requested by local authorities. Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchidectomy or vasectomized with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

Female partners are considered to be of childbearing potential unless 1 of the following applies:

- Is postmenopausal, defined as no menses for at least 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: or
- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy.

Male patients of reproductive potential must practice highly effective methods (failure rate < 1% per year) of contraception with their female partners, if of reproductive potential, during treatment and for 3 months following the last dose of study drug or longer if requested by local authorities. Highly effective contraception includes:

- Ongoing use of progesterone only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon);
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable.

Patients will be instructed to notify the investigator if pregnancy of a female partner is discovered either during or within 3 months of completing treatment with study drug.

6.5 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

7 STUDY TREATMENT(S)

7.1 Description of Treatment(s) and Storage

This study will assess the investigational drug rucaparib

Rucaparib camsylate (also known as CO-338) 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 the sponsor. A brief description of the investigational product is provided below with details in the Pharmacy Guidelines.

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 high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive one or more strengths.
Storage Conditions:	15 to 30° C (59 to 86° F).

7.2 Packaging and Labeling

7.2.1 Rucaparib

Rucaparib tablets are provided in 60-count high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers between 15° to 30° C (59° to 86° F). Patients will be dispensed 1 or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply at least 28 days of treatment until the next study drug dispensation visit.

Rucaparib bottles will be labelled in accordance with local regulatory requirements.

7.3 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive rucaparib at an initial dose of 600 mg BID.

7.4 Preparation and Administration of Protocol-specified Treatment

The starting dose of rucaparib is 600 mg ingested BID. Patients may take rucaparib with or without food. Each dose should be taken with at least 8 oz (240 mL) of water. Tablets should be swallowed whole without crushing or chewing.

Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled

time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

Dosing with rucaparib may be held or reduced as described in Section 7.4.2 and Section 7.4.3.

Patients will be provided a sufficient quantity of study drug for 28 days until the next study drug dispensation visit. Patients will be instructed to bring their rucaparib tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

7.4.1 Dietary and General Restrictions

All patients participating in the study should be instructed to use caution with CYP2C9, CYP2C19, and CYP3A substrates noted in Appendix 5.

Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they burn more easily during treatment with rucaparib. When outdoors, patients should use typical precautions such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

7.4.2 Rucaparib Dose Modification 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.
- At the discretion of the investigator, rucaparib may be held or continued if new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur and while evaluation to rule out pneumonitis or confirm such a diagnosis as well as etiology are ongoing; these events 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.

<u>Management of Anemia Including Evaluation for MDS/AML and Follow-up of Patients Who Discontinue Treatment with Ongoing Anemia:</u>

- If the patient develops anemia CTCAE Grade ≥3, rucaparib treatment should be held until the anemia resolves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.

  - If a patient has persistent CTCAE Grade 3 anemia despite study drug interruption, and the anemia is considered related to the patient's underlying prostate cancer (eg, patient has extensive bony disease or history of disease-related anemia), then resumption of study drug may be considered, if the patient was benefiting from treatment in opinion of the investigator

- 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, after 42 days of interruption of rucaparib, the anemia has not recovered 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).

<u>Management of Rucaparib Treatment-emergent ALT/AST Elevations:</u>

- Grade 4 ALT/AST elevations: hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction. Monitor liver function tests weekly for 3 weeks after rucaparib 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 rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN.
  - If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity resolves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction

steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor.

Drug-induced liver injury (DILI) is described in the U.S. Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation[45] and should be referenced when managing treatment-emergent ALT/AST elevations.

Rucaparib treatment must be interrupted if biochemical criteria for suspected DILI are met, according to presence of the following laboratory abnormalities:

ALT or AST > 3x ULN
and
Bilirubin > 2x ULN

While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, coadministration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, rucaparib must be permanently discontinued.

All cases of possible DILI must be reported as SAEs (see Section 10.9) and will be followed until all abnormalities have returned to normal or to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and bilirubin.

Management of New or Worsening Pulmonary Symptoms:

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high resolution CT scan) in consultation with a pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with rucaparib may be interrupted or continued per investigator discretion.

Following investigation, if pneumonitis is not confirmed, treatment with rucaparib may be resumed/continued as deemed appropriate by the investigator and in accordance with the study protocol directions for management of AEs. All confirmed events of pneumonitis should be treated as appropriate per medical judgement and institutional guidelines. If the event resolves and retreatment with rucaparib is being considered, please consult the Sponsor's Medical Monitor. Retreatment with rucaparib may be resumed at the current or a reduced dose, if appropriate.

Refer to Sections 10.3 and 10.7 of the protocol for additional information regarding classification and reporting of pneumonitis (and associated events) as an AESI.

7.4.3 Rucaparib Dose Modification

Dose reduction steps are presented in Table 4.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the Investigator.

Dose modifications (interruption, reduction, and re-escalation) must be recorded for each patient in the appropriate section of the eCRF.

Table 4. Rucaparib Dose Reduction Steps

Starting Dose	600 mg BID
Dose Level – 1	500 mg BID
Dose Level – 2	400 mg BID
Dose Level – 3*	300 mg BID

Abbreviation: BID = twice a day.

*Consult with the sponsor's medical monitor before reducing to dose level 3. Further dose reduction may be possible, but requires consultation with the sponsor's medical monitor.

7.4.4 Treatment with Rucaparib beyond Disease Progression

Patients will receive rucaparib until confirmed radiologic disease progression as assessed by investigator using modified RECIST Version 1.1 (Appendix 2) and/or PCWG3 (for bone lesions only) (Appendix 2) criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, or withdrawal of consent. However, if a patient receiving rucaparib has met criteria for confirmed radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 criteria, but the patient continues to derive clinical benefit per the investigator, then continuation of treatment will be permitted with additional consent. Clinical scenarios where continuation of study drug treatment after radiographic progression may be considered include 1) a patient for whom radiographic progression develops slowly while disease-related symptoms remain well controlled, 2) a patient who experiences progression in a site of disease that is unlikely to adversely affect prognosis (eg, enlargement of a solitary lymph node), or 3) a patient with general disease control but limited progression in sites of disease that can be managed with local therapies such as surgery or radiation. Patients continuing to receive rucaparib will continue to have all protocol-required assessments as described in Section 9, with the exception of radiographic assessments which may be performed per local standard of care.

7.5 Blinding/Masking of Treatment

This is an open-label study; the investigational product will not be blinded or masked. All patients enrolled will receive rucaparib.

7.6 Treatment Compliance

Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to keep all unused containers (empty, partially used, and/or unopened) for accountability and bring them back at the next scheduled clinic visit. A compliance check and tablet count will be performed by study personnel. Study site personnel will record compliance information on the electronic case report form (eCRF).

Every effort should be made to ensure patients return to the clinic with their study drug containers/unused study drug at each study drug dispensation visit. Study site personnel should conduct a verbal review of dosing with the patient and document the discussion in the patient's medical record. This may serve as source documentation for the purpose of entering dosing data on the appropriate eCRF.

7.7 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation for study drug provided by the sponsor. An Interactive Web Response System (IWRS) will be used to manage study drug inventory at all sites. In order to function properly, the system will require real-time entry of study drug receipt, dispensation, destruction, patient treatment discontinuation, etc. by study personnel at the study site.

The site is responsible for the return or destruction of study drug supplied by the sponsor as required. Authorization to destroy study drug at the site that has not been dispensed to a patient (eg, expired study drug), must be requested from the sponsor prior to destruction. Any study drug supplied by the sponsor that is destroyed, accidentally or deliberately, must be accounted for. All study drug containers must be accounted for prior to their destruction at the study site, according to institutional procedures for disposal of cytotoxic chemotherapeutic drugs. Unused study drug containers should be destroyed by the site if possible. If destruction by the site is not possible, supply should be returned to the drug depot.

During the course of the study and at completion of the study, the number of study drug containers received, dispensed, returned, and destroyed must be reconciled.

8 PRIOR AND CONCOMITANT THERAPY

Patients who have received prior treatment with a PARP inhibitor including IV or oral rucaparib, mitoxantrone, cyclophosphamide or any platinum-based chemotherapy are not eligible to participate in this study.

Patients are required to have progressed after 1 prior line of taxane-based chemotherapy in the castration-resistant setting; patients who have progressed after 2 lines of taxane chemotherapy in the castration-resistant resistant setting are not eligible to participate in this study. However, an incomplete course of taxane chemotherapy (eg, stopping due to intolerance or stopping for reasons other than disease progression) will not be counted towards this limit.

All procedures performed (eg, thoracentesis, etc.) and medications used during the study must be documented on the eCRF.

8.1 Supportive Care

During the study, supportive care (eg, antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. Supportive care must be recorded for each patient in the appropriate section of the eCRF.

Continuation of low-dose corticosteroid therapy that has been stable prior to study entry is permitted (see Section 6.3). A low dose is considered 5-15 mg/day of prednisone or prednisolone, and 0.5-3 mg/day of dexamethasone.

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered per standard of care and according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.2 Radiotherapy

Palliative radiotherapy for the treatment of painful bony metastasis is permitted during the study. Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation-related toxicity.

8.3 Luteinizing Hormone-releasing Hormone (LHRH) analogs

For patients who have not undergone an orchiectomy and are currently being treated with luteinizing hormone-releasing hormone (LHRH) analogs at the time of consent, therapy must be continued throughout the study.

8.4 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study. Prior treatment with anticancer therapies must have been completed at least 14 days prior to the first

dose of rucaparib. Prior treatment with hormonal therapies (with the exception of LHRH analog) must be discontinued at least 7 days prior to the first dose of rucaparib.

8.5 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the CYP interaction clinical study CO-338-044, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients taking concomitant medicines that are substrates of CYP1A2, CYP2C9, and/or CYP3A with narrow therapeutic windows (Appendix 5). Patients taking phenytoin, a CYP2C9 substrate with a narrow therapeutic window, should have therapeutic drug level monitored while using concomitantly with rucaparib.

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.

8.6 Therapies to Control Bone Loss

Patients cannot have initiated denosumab or bisphosphonate therapy or adjusted bisphosphonate or denosumab dose/regimen within 4 weeks prior to first dose of rucaparib. Patients on a stable denosumab or bisphosphonate regimen are eligible and may continue treatment. Initiation of bisphosphonates or other approved bone targeting agents if clinically indicated is allowed, and should not result in study treatment discontinuation unless patient has radiographic evidence of disease progression.

8.7 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin). Patients taking warfarin should have INR monitored regularly per standard clinical practice.

8.8 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Rucaparib marginally increased digoxin AUC by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored regularly via standard clinical practice.

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.

9 STUDY PROCEDURES AND ACTIVITIES BY VISIT

9.1 Schedule of Assessments

Table 5 summarizes the procedures and assessments to be performed for all patients. Study procedures and assessments should be performed as close to the scheduled time as possible, but within ±3 days of the scheduled time unless otherwise stated.

Table 5. Schedule of Assessments

		Screening Phase		Treatment Phase					Post-Treatment Phase		
				Week 1	Week 3	Week 5	Week 7	Week 9 & every 4 weeks thereafter			
Procedure[a]	**Pre-screening Phase**	**Day -28 to Day -1**	**Day -14 to Day -1**	**Study Day 1[b]**	**Study Day 15**	**Study Day 29**	**Study Day 43**	**Day 57 & every 28 days thereafter**	**Treatment Discontinuation**	**28-day Follow-up**	**Long-term Follow-up**
Informed Consent	X[c]	X									
BRCA, ATM or other HRR gene mutation assessment from ctDNA blood and tumor sample[c, d]	X[c]										
Medical/Oncology History[e]		X									
Blood samples for plasma ctDNA analysis[f]		X		X		X		X	X		
Physical Examination, Weight, Height[g]		X		X	X	X	X	X	X	X	
Vital Signs[h]		X		X	X	X	X	X	X	X	
12-lead ECG[i]		X							X		
Prior/Concomitant Medications/Procedures		X		X	X	X	X	X	X	X	
Tumor Assessment/CT/MRI and Bone Scan[j]		X		End of every 8 weeks from Study Day 1, up to 24 weeks (Study Weeks 9, 17, 25) and then every 12 weeks thereafter (Study weeks 37, 49, 61, etc.)[k]					X[l]	X[l]	X[l]
Archival Primary/ Metastatic Tumor Tissue Sample for retrospective testing[m]		X									
Patient-reported outcome (BPI-SF, analgesic drug score, FACT-P, EQ-5D-5L)[n]			X	X		X		X	X	X	X
ECOG Performance Status			X	X	X	X	X	X	X	X	
Serum Testosterone		X									
PSA Measurement[o]		X		X		X		X	X		
Clinical Laboratory Assessments[p]			X	X	X	X	X	X	X	X	
Pharmacogenomic blood sample[q]				X							
Study Drug Dispensation				X		X		X			
Adverse Events[r]	(X)	(X)	(X)	X	X	X	X	X	X[s]	X[s]	
Plasma PK Sample						X[t]		X[t]			

Post-progression Tumor Biopsy (Optional)									X[u]		
Subsequent Treatments, AESIs, & Survival[v]										X	X

Abbreviations: AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine transaminase, AML = acute myeloid leukemia, ANC = absolute neutrophil count, AST = aspartate transaminase, ATM = ataxia telangiectasia mutated serine/threonine kinase, BPI-SF = Brief Pain Inventory – Short Form, BRCA = breast cancer 1 or breast cancer 2, BUN = blood urea nitrogen, CO_2 = bicarbonate, CR = complete response, ctDNA = circulating cell-free tumor DNA, CT = computer tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EQ-5D-5L = Euro-QoL 5 dimensions 5 level questionnaire, FACT-P = Functional Assessment of Cancer Therapy-Prostate, Hct = hematocrit, HDL= high density lipoprotein, HDP = hydroxydiphosphonate, Hgb = hemoglobin, HRR = homologous recombination repair, INR = international normalized ratio, LDL= low density lipoprotein, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MDP = methylene diphosphonate, MDS = myelodysplastic syndrome, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response, PSA = prostate-specific antigen, PV = Pharmacovigilance, RBC = red blood cell count, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = serious adverse event, WBC = white blood cell

[a] = The study visit window is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the patient's rucaparib supply.

[b] = First dose of rucaparib is designated as Study Day 1. Procedures required on Study Day 1 may be omitted if completed **≤ 3 days earlier during the screening period with the exception of ctDNA which will be collected during Pre-Screening and must be collected during Screening and on Study Day 1**.

[c] = Pre-Screening is for central testing of plasma ctDNA and tumor tissue samples to identify patients with qualifying deleterious HRR gene mutations. To enter Pre-Screening, patients should have evidence of radiographic or biochemical disease progression, and be eligible for this study as their immediate next therapy. Both plasma ctDNA and tumor tissue samples should be submitted simultaneously. If plasma or tissue testing results in failure, additional samples may be submitted, as available. Pre-Screening requires a separate informed consent form.

[d] Tissue for Pre-Screening should be from biopsy or resection specimen of metastatic tumor, if there is a lesion suitable for biopsy. A biopsy or resection of a visceral or nodal site of metastasis is preferred; however a biopsy of primary tumor or of a site of bony metastasis is also acceptable. If a metastatic biopsy is not feasible, archival tissue samples can be submitted. Archival tissue for Pre-Screening should be < 3 years old. Submission of a tumor block with a tumor content ≥ 30% with a minimum of 80% nucleated cellular content should be provided.

[e] = Includes demographic information. Patient's medical record must include prior treatments received, dates of administration, date of progression and how assessed, PSA and radiology reports.

[f] = Blood samples for plasma ctDNA analysis during Screening, before dosing on Study Day 1, and every 28 days thereafter are for pharmacodynamic assessments and companion diagnostic development. Plasma ctDNA is required on Study Day 1 even when it was previously collected.

[g] = Height at screening only.

[h] = Vital signs (blood pressure, pulse, and temperature) to be taken on drug administration days, after the patient has been resting for at least 5 minutes.

[i] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.

[j] = Tumor assessments to consist of clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen and pelvis, with appropriate slice thickness); CT with contrast is preferred, non-contrast may be used where clinically indicated. MRI may be used in place of CT scan if requested by local authorities. Where indicated for neurological symptoms, MRI of spine and skull to be conducted. Radionuclide bone scanning (whole body) using 99mTc-MDP or HDP. Other studies, such as PET/CT, may also be performed. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.

[k] = Disease assessment by CT/MRI and bone scans will be performed during screening, during the treatment phase, and Treatment Discontinuation, and if applicable, during follow up. Modified RECIST 1.1/PCWG3 criteria will be used. If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented.

[l] = Radiologic assessments should continue for all patients until confirmation of radiographic progression per investigator assessment, including any patient who discontinued from study treatment for reason other than disease progression or death. Tumor assessments should be performed during the Treatment Discontinuation visit, 28-day Follow-up, or during Long-term Follow-up if the reason was other than radiologically confirmed disease progression and it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment. Tumor assessments should continue on schedule (ie, every 8 or 12 weeks) during Long-term Follow-up until radiographically confirmed disease progression.

[m] = If archival primary or metastatic tumor tissue was not submitted during Pre-Screening, a specimen should be submitted during the Screening period or after enrollment for retrospective testing by the central laboratory. Archival tissue submitted during Screening for retrospective testing can be > 3 years old. Refer to the Pathology Charter for detailed sample handling instructions.

[n] = The BPI-SF, analgesic drug score, FACT-P, and EQ-5D-5L instruments should be completed prior to other scheduled study procedures and dosing (if applicable). During long term follow up, if possible, PROs to be collected to coincide on days when tumor assessments are performed.

[o] = All PSA measurements are performed by the local laboratory. Serial PSA measurements that show progression at study entry must follow the protocol specification.

[p] = Clinical laboratory assessments will be done locally. Hematology should include RBC and parameters (Hgb, Hct, MCV, MCH, MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count. Serum chemistry should include total protein, albumin, creatinine for estimating GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, LDH, lipid panel (total cholesterol, LDL, HDL, and triglycerides), glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Fasting is not required. Urinalysis should include protein, glucose, blood, pH, and ketones. Microscopic evaluation to assess abnormal findings, if clinically warranted by investigator.

[q] If pharmacogenomic sample is not collected on Study Day 1, it must be collected as soon as possible thereafter.

[r] = AEs occurring after first dose of rucaparib through to 28 days after last dose of rucaparib will be recorded. In addition, SAEs that were related to a Pre-Screening or Screening procedure will also be reported.

[s] = Ongoing SAEs, AESIs and Grade 3/4 AEs will be followed to resolution or stabilization. SAEs/AESIs are collected per Clovis PV guidelines and reported in the Clovis PV database through the 28-day Follow-up Visit after the last dose of rucaparib. Ongoing SAEs and AESIs at the time of the 28-day Follow-up Visit will be followed to resolution, stabilization, or lost to follow-up. After this visit, only SAEs considered as potentially related to study drug (including serious reports of pneumonitis or associated events, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, will be reported.

[t] = PK within 1 hr prior to the morning dose on Study Day 29, Day 57, Day 85, and Day 113. The PK sample should be collected close to 12 hours post the last dose (even if the morning dose on the specified visit days is not administered).

[u] = Optional tumor biopsy should be collected from patients at time of disease progression. Refer to the Pathology Charter for detailed sample handling instructions.

[v] = All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments and survival every 12 weeks relative to the last dose of rucaparib until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone and can be completed to coincide with scheduled tumor assessments and/or PRO during this period.

9.2 Informed Consent

Patients are required to sign the Pre-Screening ICF prior to undergoing any Pre-Screening activities (ie, deleterious HRR gene mutation testing), and are required to sign the Screening ICF prior to undergoing any other Screening assessments. Obtaining written informed consent does not signify the start of the Screening Phase as it begins when the first study-specific screening activity is performed.

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. The information on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand.

Additionally, patients undergoing tumor tissue biopsy during Pre-Screening or at the time of radiologic disease progression/treatment discontinuation must provide additional consent for this procedure.

Patients with radiologic disease progression who are still receiving benefit and are allowed to continue rucaparib treatment must also provide consent for continued treatment.

9.3 Pre-Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to Screening. Pre-Screening procedures may be repeated in the event of test failure.

Pre-Screening is for central testing of plasma ctDNA and tumor tissue samples to identify patients with qualifying deleterious HRR gene mutations. Patients with eligible deleterious HRR gene mutations identified through local testing need not enter Pre-Screening. To enter Pre-Screening, patients should have evidence of radiographic or biochemical disease progression, and be eligible for this study as their immediate next therapy. Patients must sign the Pre-Screening informed consent form.

During Pre-Screening:

- Submit patient plasma for ctDNA analysis and tissue samples simultaneously
- Tissue should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy. A biopsy or resection of a visceral or nodal site of metastasis is preferred; however, a biopsy of primary tumor or of a site of bony metastasis is also acceptable
- If a metastatic biopsy is not feasible, archival tissue samples can be submitted. Archival tissue should be < 3 years old. The most recently collected tumor tissue sample available that is of adequate quality (at least 30% tumor content with a minimum of 80% nucleated cellular content) should be provided
- If plasma or tissue samples result in test failure, sites are encouraged to submit additional samples, as available, in order to obtain a successful test result

A central laboratory test result or a local laboratory test result is required for subsequent Screening of these patients

Refer to the Pathology Charter for detailed tissue sample handling instructions

SAE monitoring is ongoing during Pre-Screening (only report if related to screening procedures)

9.4 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to enrollment within the allowable windows of time as indicated below. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care. Screening procedures may be repeated if the findings/results are considered invalid or not representative of the patient's baseline medical status. When screening procedures are repeated, the rationale should be documented in the source file.

9.4.1 Screening: Up to 28 days Prior to Start of Treatment

- Serum testosterone level measurement
- PSA measurement
- Medical/oncology history, including demographic information
- Plasma sample for ctDNA
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and body temperature)
- 12-lead ECG
- Prior and concomitant medications, any surgical/medical procedures
- Tumor assessment: assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET]/CT, and ultrasound) may be performed if required. Radionuclide bone scanning (whole body) should be performed using 99mTc-methylene diphosphonate (MDP) or hydroxydiphosphonate (HDP). The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study.
    - If a patient has known brain metastases, this disease should be evaluated at each required assessment time
- Archival primary and metastatic tumor tissue (if available, and not already submitted to the central laboratory) for retrospective testing by the central laboratory. Archival tissue samples > 3 years old are allowed for retrospective testing purposes. Samples may be submitted after enrollment. Refer to the Pathology Charter for detailed tissue sample handling instructions.
- SAE monitoring (only report if related to screening procedure)

9.4.2 Screening: Up to 14 days Prior to Start of Treatment

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9); should be completed before other procedures
- Hematology
- Serum chemistry. Note: fasting is not required
  - Estimated GFR using Cockcroft-Gault formula (Appendix 4)
- Urinalysis (performed on freshly voided clean sample)
- ECOG performance status (Appendix 3)
- SAE monitoring (only report if related to screening procedure)

9.5 Treatment Phase

During the treatment period, patients will receive oral rucaparib tablets which should be taken BID at 600 mg/dose with 8 oz (240 mL) of water with or without food. In each study visit, the first dose of rucaparib will be taken in clinic, with the remaining doses self-administered by the patient at home. Patients should take rucaparib at about the same time every day. Patients will inform the clinic staff of any changes to their dose and timing of self-administration of oral rucaparib.

Unless otherwise specified, all patients will undergo the following procedures and assessments.

9.5.1 Study Day 1 (Week 1)

The following procedures will be completed before rucaparib is administered, unless if completed ≤ 3 days earlier during the screening period in which case they may be omitted:

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9; should be completed before other procedures)
- Physical examination
- Weight
- Vital signs
- Concomitant medications and procedures
- PSA measurement
- ECOG performance status (Appendix 3)
- Hematology
- Serum chemistry (fasting is not required)

- Urinalysis
- Plasma sample for ctDNA (required on Study Day 1 even if collected at any time during the Pre-Screening or Screening Phase)
- Blood sample for pharmacogenomic analysis
- AE monitoring
- Dispensation of rucaparib.

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until the next study drug dispensation visit. Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.4.2.

Site personnel will account for all rucaparib that is administered or dispensed to the patient during the study visit and document appropriately.

9.5.2 Study Day 15 (Week 3)

The following procedures will be completed:

- Physical examination
- Weight
- Vital signs
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- AE (inclusive of SAE and AESI) monitoring

Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.4.2.

9.5.3 Study Day 29 (Week 5)

Patients will be instructed to refrain from taking their first dose of rucaparib at home on the day of their visit to collect plasma samples for PK.

Plasma samples for PK analysis should be collected before the morning dose as close to 12 hours after the previous dose as possible. If the start of the next dose is delayed, the PK sample should still be collected during this visit instead of the delayed start of the next study visit.

The following procedures will be completed:

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9; should be completed before other procedures)
- Physical examination
- Weight
- Vital signs
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- PSA measurement
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- Plasma sample for ctDNA
- Plasma sample for PK analyses
- AE (inclusive of SAE and AESI) monitoring
- Dispensation of rucaparib

Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.4.2.

9.5.4 Study Day 43 (Week 7)

The following procedures will be completed:

- Physical examination
- Weight

- Vital signs
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- AE (inclusive of SAE and AESI) monitoring

Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.4.2.

9.5.5 Study Day 57 (Week 9) and Every 28 Days Thereafter

Patients will be instructed to refrain from taking their first dose of rucaparib at home on study visits when plasma samples are collected for PK.

Plasma samples for PK analysis should be collected before the morning dose on Study Day 57, Day 85, and Day 113 as close to 12 hours after the previous dose as possible. If the start of the next dose is delayed, the PK sample should still be collected during this visit instead of the delayed start of the next study visit;

The following procedures will be completed:

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9; should be completed before other procedures)
- Physical examination
- Weight
- Vital signs
- Tumor assessment scans at the end of every 8 calendar weeks (± 7 days) for the first 24 weeks (Weeks 9, 17, 25), and then every 12 calendar weeks (± 7 days) thereafter (Weeks 37, 49, 61, etc)
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- PSA measurement
- Hematology

- Serum chemistry (fasting is not required)
- Urinalysis
- Plasma sample for ctDNA
- Plasma sample for PK analyses (Study Day 57, Day 85, and Day 113 only)
- AE (inclusive of SAE and AESI) monitoring
- Dispensation of rucaparib

Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of water with or without food. Patients will keep all unused containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 7.4.2.

9.6 Post-treatment Phase

9.6.1 Treatment Discontinuation Visit

Upon treatment discontinuation, regardless of the reason, patients will have a Treatment Discontinuation Visit. However, patients receiving rucaparib with radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 criteria (for bone lesions), as assessed by the investigator, but still receiving benefit, per the investigator, may be considered for treatment continuation. Continuation of rucaparib treatment beyond progression will require separate patient consent. If the patient does continue to receive rucaparib, then the patient will continue treatment with rucaparib as described starting in Section 9.5.5 and a Treatment Discontinuation Visit will occur at the end of all rucaparib treatment. Patients who continue treatment with rucaparib after radiologic disease progression will have the option of tumor tissue biopsy collection at time of first disease progression on study (requires additional consent). Tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. Refer to the Pathology Charter for detailed sample handling instructions.

The following procedures will be performed:

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9; should be completed before other procedures)
- Physical examination
- Weight
- Vital signs
- 12-lead ECG

- Tumor assessment if it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment and the reason for treatment discontinuation was other than radiographically confirmed disease progression.
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- PSA measurement
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- Plasma sample for ctDNA
- AE (inclusive of SAE and AESI) monitoring
- Optional tumor tissue biopsy collection after the time of disease progression (radiologic or clinical) and prior to initiation of any subsequent anticancer therapy (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to Section 9.11 for more information and to the Pathology Charter for detailed sample handling instructions.

9.6.2 28-Day Follow-up Visit

The following procedures will be performed for all patients at 28 (±3) days after the last dose of rucaparib.

- PRO collected using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9; should be completed before other procedures)
- Physical examination
- Weight
- Vital signs
- Tumor assessment only if it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment for those patients that have not had radiographic progression confirmed by investigator assessment
- Concomitant medications and procedures
- ECOG performance status (Appendix 3)
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- AE (inclusive of SAE and AESI) monitoring

- Information collected for subsequent treatments.

Patients who do not withdraw from the study at this visit will continue with long-term follow-up as described in Section 9.6.3.

9.6.3 Long-term Follow-up

Patients who complete a 28-Day Follow-up Visit after the last dose of rucaparib will continue in long-term follow-up as described below.

- If applicable, tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) when the reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since last scan or disease progression was noted on the last scan. Tumor assessment should continue to be performed at the end of every 8 calendar weeks (± 7 days) relative to Study Day 1 (Week 1) up to 24 weeks, then every 12 calendar weeks (± 7 days), until confirmed radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, as assessed by the investigator, loss to follow-up, withdrawal, or study closure.
  - PRO assessments will also continue and coincide on days when tumor assessments are performed until confirmed radiographic disease progression. PRO using the BPI-SF (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9)
- All patients discontinued from treatment, regardless of reason, will be followed and information collected for subsequent treatments and survival every 12 weeks from last dose of rucaparib until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone and can be completed to coincide with scheduled tumor assessments and/or PRO during this period.
- SAEs related to study drug and AESIs are to be reported as specified in Section 10.7.

9.7 Methods of Data Collection

9.7.1 Medical History and Demographic/ Baseline Characteristics

Basic demographic and baseline characteristics will be collected during screening. In addition to the evaluation of a patient's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events that occur after signing of informed consent but prior to initiation of rucaparib, unless serious and due to a protocol-mandated procedure, should be recorded on the Medical History eCRF.

The patient's entire oncology history will be collected on the appropriate eCRF including date of diagnosis for mCRPC (and other malignancy, if applicable), prior surgeries/treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, and BRCA/ATM/other HRR gene mutation status (if known).

9.8 Prior and Concomitant Medication Assessments

Medications being used by the patient will be recorded as prior medications during screening and as concomitant medications following receipt of the first dose of rucaparib through the completion of the 28-day Follow-up Visit after treatment discontinuation. Medication information will be entered in the appropriate eCRF after it is obtained at each study visit.

9.9 Efficacy Evaluations

Soft tissue (visceral and nodal) disease will be evaluated for evidence of radiographic response based on modified RECIST 1.1 criteria (Appendix 2). Bone lesions will be followed and evaluated for evidence of radiologic progression based on PCWG3 criteria (Appendix 2). Additionally, PSA response will be evaluated using sequential PSA samples.

Tumor assessments will be performed during screening (baseline), at the end of every 8 calendar weeks (±7 days) relative to Study Day 1 (Week 1) up to 24 weeks, then every 12 calendar weeks (±7 days), until confirmed radiologic disease progression by modified RECIST Version 1.1 and/or PCWG3 (for bone lesions only) criteria, as assessed by the investigator, loss to follow-up, withdrawal, or study closure. Tumor assessments should be performed at the time of treatment discontinuation, at the 28-day Follow-up visit, or during Long-term Follow-up if the reason was other than radiologically confirmed disease progression and it has been ≥ 8 weeks (≥ 12 weeks if previous scan was after 24 weeks on study) since the last assessment. Tumor assessments should continue on schedule (ie, every 8 or 12 weeks) during Long-term Follow-up until radiographically confirmed disease progression. If a CR or PR is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented.

Tumor assessments should consist of clinical examination and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (MRI, X-ray, PET/CT, and ultrasound) may also be performed if required. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. Radionuclide bone scanning (whole body) should be performed using 99mTc-MDP or HDP. All sites of disease should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time.

Copies of CT scans (and other imaging, as appropriate) will be collected from all patients for IRR.

9.10 Safety Evaluations

9.10.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. During the Pre-Screening Phase and Screening Phase, unless otherwise required by local regulations, SAEs which are related to protocol-mandated

assessments will be reported. Once enrolled and rucaparib is administered, patients will be monitored for all AEs/SAEs/AESIs during study participation and until 28 days after the last dose of rucaparib. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization. After the 28-day window, only SAEs considered as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the 28-Day Follow-up Visit (28-days after the last dose of rucaparib).

AEs and laboratory abnormalities will be graded according to the National Cancer Institute CTCAE grading system (Version 4.03 or higher) and recorded on the eCRF.

Complete details for monitoring AEs (inclusive of SAEs and AESIs), including the definition of drug-related AEs, are provided in Section 10.

9.10.2 Clinical Laboratory Investigations

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

Hematology: red blood cells (RBC) and parameters (hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]) and reticulocyte count, white blood cells (WBC) and differential (with ANC), and platelet count will be assessed at screening, during treatment at each study visit, at the Treatment Discontinuation Visit, and 28-day Follow-up 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: total protein, albumin, creatinine for estimating GFR using the Cockcroft-Gault formula (Appendix 4), BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), glucose, sodium, potassium, chloride, CO_2, calcium, phosphorus, and lipid panel (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides), at screening, during treatment at each study visit, at the Treatment Discontinuation Visit, and 28-day Follow-up 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. Additional and more frequent tests may be performed at the investigator's discretion.

Urinalysis: performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will

be performed at screening, during treatment at each study visit, at the Treatment Discontinuation Visit, and 28-day Follow-up Visit for all patients, but may be conducted at other times as clinically indicated.

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 will be documented on the eCRF as an AE. Refer to Section 10.5 for guidelines on reporting of abnormal laboratory values as AEs.

9.10.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature and will be taken after the patient has been resting for at least 5 minutes during screening, at study visits during the Treatment Phase, at the Treatment Discontinuation Visit and the 28-Day Follow-up Visit.

9.10.4 12-Lead Electrocardiogram

For all patients, 12-lead ECGs will be performed at the following times:

- Screening (within 28 days prior to enrollment)
- Treatment Discontinuation Visit

The following will be measured or calculated: heart rate, PR, QRS, QT, QTc, and rhythm. The investigator or qualified designee will review the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

If it is clinically indicated, ECGs can be performed at other times during the study.

9.10.5 Body Weight and Height

Height will be measured during the screening visit only. Weight will be measured per institutional guidelines during screening, during treatment at each study visit, at the Treatment Discontinuation Visit, and the 28-Day Follow-up visit.

9.10.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed during screening and at treatment discontinuation. Physical examinations at study visits during the Treatment Phase and 28-Day Follow-up Visit will be limited as appropriate.

9.10.7 ECOG Performance Status

ECOG performance status (Appendix 3) will be assessed during screening, at study visits during the Treatment Phase, at the Treatment Discontinuation Visit and 28-Day Follow-up Visit. The ECOG performance status should be assessed by the same study personnel at each visit, if

possible. For eligibility purposes, patients with borderline ECOG performance status should be considered carefully to avoid enrolling patients who may have significant impairment.

9.11 Biomarker Analysis – FFPE Tumor Tissue

An optional tumor biopsy obtained between the time of disease progression/treatment discontinuation and the start of the next treatment will be obtained from consenting patients. The molecular profile of the progression biopsy will be compared with that from pretreatment primary or metastatic tumor tissue to identify mechanisms of resistance to rucaparib. Patients must provide additional consent for the optional tumor tissue biopsy sample. New lesions or lesions that are growing should be prioritized for the optional biopsy. If possible, collect the lesion responsible for progression. Detailed sample handling instructions are located in the Pathology Charter.

9.12 Biomarker Analysis – Blood

Blood samples for plasma ctDNA will be collected during Pre-Screening (for deleterious BRCA, ATM, or other HRR gene mutation assessment), Screening, before dosing on Study Day 1, every 28 days thereafter, and at treatment discontinuation from all patients entered in the study. Blood samples for pharmacogenomics analyses will be collected on Study Day 1 from all patients entered in the study. Genomic DNA will be extracted from the cellular portion of this blood sample and analyzed to determine whether the deleterious BRCA/ATM/other HRR gene mutation is germline or somatic prior to final data analysis. Because the germline analysis will be done near the end of the study, there are no plans to share these results with the investigator. However, if an actionable mutation, as defined by the American College of Medical Genetics and Genomics (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/), is revealed that was not detected in tumor or plasma, these incidental finding will be made available to the investigator provided the results are generated from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Sample collection details will be provided in a Laboratory Manual.

9.13 Pharmacokinetics Evaluation

Plasma samples are to be collected for trough level PK analysis of rucaparib 1 hour before the morning dose on Study Day 29, Day 57, Day 85, and Day 113. If the start of the next dose is postponed or suspended, the PK sample should be collected as close to 12 hours after the previous dose as possible. Refer to the Laboratory Manual for sample collection details for PK samples.

9.14 Patient Reported Outcomes (Health and Quality of Life Questionnaires)

Patient reported outcomes utilizing the BPI-SF, (Appendix 6), FACT-P (Appendix 7), EQ-5D-5L (Appendix 8), and analgesic drug score instruments (Appendix 9) will be assessed during screening, Study Day 1 and every 28 days thereafter, at the Treatment Discontinuation Visit, at the 28-Day Follow-up Visit, and if applicable, during long term follow-up. The analgesic drug score will be recorded according to the WHO's analgesic ladder: 0 for no analgesic, 1 for nonopioids, 2 for opioids for moderate pain, and 3 for opioids for severe pain.[46]

Patients should complete the instruments before any other scheduled study procedures are performed and dosing occurs (if applicable). For patients who discontinued treatment prior to radiologic disease progression, PRO assessments should be collected until subsequent radiologic disease progression was documented.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug interaction 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 monitor all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (eg, "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).

10.2 Definition of a Serious Adverse Event

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 rucaparib 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. This excludes death due to progression of patient's underlying cancer. (refer Section 10.4);
- 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.

10.3 Definition of an Adverse Event of Special Interest

AESIs (serious or nonserious) are defined as AEs of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor **within 24 hours** of knowledge of the event (see Section 10.7 for reporting instructions).

10.4 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:

- Preplanned or elective hospitalization including social and/ or convenience situations (eg, respite care);
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward);
- Overdose of either Clovis study drug or concomitant medication unless associated with an SAE. However, the event should still be captured as a nonserious 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) and progression of disease leading to death should not be reported as an AE or SAE. This section excludes other SAEs with fatal outcome;
- Events that meet the SAE criteria (as outlined in Section 10.2) and occur after informed consent but before the first dose of study drug, which are considered unrelated to protocol-mandated procedures.

10.5 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 1 of the following criteria is met:

- an action on rucaparib treatment 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

10.6 Pregnancy or Drug Exposure During Pregnancy

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a partner of a study patient during study participation or within 3 months of last dosing must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE.

A pregnancy will be followed through to outcome. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form is to 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.

10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Events that occur after signing of informed consent but prior to initiation of rucaparib, unless due to a protocol-mandated procedure, are to be recorded on the Medical History eCRF; however, events are to be reported as SAEs if serious and related to a protocol-mandated procedure during the Pre-Screening Phase or Screening Phase.

Any AE that occurs after first dose of rucaparib through 28 days after receiving the last dose of rucaparib will be recorded on the AE eCRF.

Report any AE of pneumonitis, or any of the following AEs, irrespective of causality assessment and severity, as an AESI within 24 hours using the study Serious Adverse Event Form:

- Pneumonitis
- Interstitial lung disease
- Pulmonary fibrosis
- Acute interstitial pneumonitis
- Alveolitis necrotizing
- Alveolitis
- Hypersensitivity pneumonitis
- Organizing pneumonia

After the 28-day Follow-up Visit, only SAEs assessed as potentially related to rucaparib should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28-days after the last dose of rucaparib).

Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.8.

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 causal relationship to rucaparib, severity, and seriousness. The action taken and the outcome must also be recorded.

SAEs and AESIs that occur during the study or within 28 days after receiving the last dose of rucaparib, whether or not related to rucaparib, must be reported immediately (ie, **within 24 hours** of knowledge of the event or additional information for a previously-reported event) to the sponsor/ SAE designee. The contact information for reporting of SAEs/AESIs can be found on the SAE/AESI Reporting Form.

10.7.1 Onset Date of Adverse Events

The onset date is the date that the event or the signs/symptoms attributed to the event started.

10.7.2 Resolution Date of Adverse Events

The resolution date is the date that the event or the signs/symptoms attributed to the event resolved or resolved with sequelae or it is the date when the patient has reached a new baseline if the event is not expected to resolve.

10.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, Version 4.03 or higher grading scale (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).[47]

Severity is not the same as Serious.

For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- Mild events are usually asymptomatic or have mild symptoms with clinical or diagnostic observations only; intervention is not indicated
- Moderate events introduce a low level of inconvenience or concern to the patient, local or noninvasive intervention may be indicated, and may interfere with age-appropriate daily activities

- Severe events are medically significant, but not immediately life-threatening; interrupt the patient's usual self-care daily activities, disabling, and hospitalization (or prolongation of hospitalization) is indicated
- Life-threatening events require urgent intervention to prevent death; or
- Fatal events are those events that lead to the patient's death

10.7.4 Causal Relationship of Adverse Events to Rucaparib

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, and dechallenge or rechallenge with rucaparib.

Not Related to Rucaparib	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of rucaparib • It does not follow a known pattern of response to rucaparib • It does not reappear or worsen when rucaparib is restarted, or • An alternative explanation is likely, but not clearly identifiable.
Related to Rucaparib	• An AE that is difficult to assign to alternative causes • It follows a strong or reasonable temporal sequence from administration of rucaparib • 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 rucaparib, or • It is confirmed with a positive rechallenge or supporting laboratory data.

10.8 Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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, death, or until lost to follow-up. After the 28-day window, only SAEs considered as potentially related to rucaparib (including serious reports of pneumonitis or associated events, if considered to be related to rucaparib), and AESIs of MDS and AML, irrespective of causality, should be reported.

10.9 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria (see Section 7.4.2),[45] must be reported as SAEs (see Section 10.7 for reporting details).

10.10 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report. For reporting SAEs/AESIs or pregnancies, use the applicable report forms. The contact information for reporting of SAEs/AESIs or pregnancies can be found on each of the forms.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

11 PLANNED STATISTICAL METHODS

11.1 General Considerations

Efficacy analyses will be presented separately for each Cohort and, if applicable, cohorts may be combined. Safety analyses will be presented separately for each Cohort and also combined for all patients who received at least one dose of protocol-specified treatment.

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the 25^{th}, 50^{th} (median), and 75^{th} percentiles with the 95% confidence interval will be summarized.

The number of patients with events and the number of censored patients will also be presented.

Further details to describe handling of missing, unused, and spurious data will be in the Statistical Analysis Plan (SAP). Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

All statistical analyses will be conducted with the SAS® System, Version 9.3 or higher. Further details around the statistical analyses planned in this study will be outlined in the SAP. Changes to or deviations from the SAP will be described in the clinical study report (CSR).

11.2 Determination of Sample Size

The enrollment planned for this study is approximately 360 patients, with up to approximately 150 patients in Cohort A with measurable visceral and/or nodal disease (ie, up to 100 patients with a deleterious BRCA1/2 mutation [with a maximum of 60 patients who have only measurable lymph node disease], and up to approximately 50 patients with a deleterious ATM mutation), up to approximately 150 patients in Cohort B (ie, up to approximately 100 patients with a deleterious BRCA1/2 mutation and 50 patients with a deleterious ATM mutation), and up to approximately 60 patients in Cohort C.

Cohort A

Cohort A will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort A (BRCA1/2)

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. Characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

In the first stage, 37 patients with a deleterious BRCA1/2 mutation will be evaluated. If the study is to proceed to the second stage, additional patients with a deleterious BRCA1/2 mutation will be accrued for a total of 83.

Note: If the study is to proceed to Stage 2, additional patients with a deleterious BRCA1/2 mutation up to 100 total patients (and a maximum of 60 patients with only measurable lymph node disease) will be enrolled in Cohort A (BRCA1/2) if additional clinical data is requested by the regulatory authorities to support regulatory filing. If sufficient evidence exists to support a regulatory filing prior to fully enrolling Cohort A (BRCA1/2), enrollment may be discontinued early.

Cohort A (ATM)

Patients in Cohort A (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort A (BRCA1/2). It is expected that about 1/3 of the Cohort A patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort A (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort A (ATM).

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. Characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

In the first stage, 31 patients with a deleterious ATM mutation will be evaluated. If the study is to proceed to the second stage, additional patients with a deleterious ATM mutation will be accrued for a total of 53.

Cohort B

Cohort B will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM). Cohort B will be enrolled concurrently with Cohort A and is expected to enroll at approximately the same rate as Cohort A. Enrollment in Cohort B will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (BRCA1/2)

A Simon 2-stage type futility rule will be employed in Cohort B (BRCA1/2). Characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

In the first stage, 19 patients with a deleterious BRCA1/2 mutation will be evaluated. If the study is to proceed to the second stage, additional patients with a deleterious BRCA1/2 mutation will be accrued for a total of 54. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 100 total, may be enrolled. Enrollment in Cohort B (BRCA1/2) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (ATM)

Patients in Cohort B (ATM), having a deleterious ATM mutation, will be enrolled concurrently with patients from Cohort B (BRCA1/2). It is expected that about 1/3 of the Cohort B patients will have deleterious ATM mutations. If 100 patients are enrolled in Cohort B (BRCA1/2), then approximately 50 patients would be expected to enroll into Cohort B (ATM).

A Simon 2-stage type futility rule will be employed. Characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

In the first stage, 18 patients with a deleterious ATM mutation will be evaluated. If the study is to proceed to the second stage, additional patients with a deleterious ATM mutation will be accrued for a total of 33. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 50 total, may be enrolled. Enrollment in Cohort B (ATM) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort C

Up to approximately 60 patients will be enrolled into Cohort C. Enrollment in Cohort C will be halted when Cohort A (BRCA1/2) is fully enrolled. Since this cohort will enroll patients that have 1 of several different deleterious HRR gene mutations, each gene will be examined separately.

11.3 Analysis Populations

The following analysis populations are defined for the study:

Safety Population – The safety population will consist of all patients who received at least 1 dose of protocol-specified treatment.

IRR Efficacy Population – The IRR efficacy population will consist of all patients evaluable for response by RECIST Version 1.1/PCWG3 criteria (Appendix 2) per independent radiology review or, for Cohort B, PSA response.

Investigator Efficacy Population – The investigator efficacy population will consist of all patients evaluable for response by RECIST Version 1.1/PCWG3 criteria (Appendix 2) per investigator or, for Cohort B, PSA response.

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for discontinuation will be summarized.

11.4 Demographics and Baseline Characteristics

All demographic (eg, age, race, and ethnicity as allowed by local regulations) and baseline characteristics will be summarized for the safety population.

The following baseline variables will be summarized with frequency tabulations:

- Time since diagnosis of primary tumor (months): 0 to 12, > 12 to 24, > 24;
- The following BRCA/ATM/other HRR gene mutation characteristics will also be summarized:
  - BRCA/ATM/other HRR gene mutation status (germline or somatic)

Descriptive statistics may also be used to summarize the continuous variables.

11.5 Efficacy Analyses

11.5.1 Primary Efficacy Analyses

For Cohort A, the primary efficacy endpoint for the study is confirmed radiologic ORR (CR or PR per modified RECIST Version 1.1 criteria and no bone progression per PCWG3 prior to a CR or PR) by central independent radiology review (IRR) in patients with measurable visceral and/or nodal disease at baseline per IRR (Cohort A). This endpoint will be summarized along with a 95% confidence interval and will be analyzed separately for patients with deleterious BRCA1/2 and ATM mutations.

An analysis of confirmed radiologic ORR by the investigator will also be conducted as supportive to the primary endpoint.

For Cohort B, the primary efficacy endpoint is confirmed PSA response (≥ 50% decrease) as assessed by a local laboratory in patients with non-measurable disease and will be summarized along with a 95% confidence interval and will be analyzed separately for patients with deleterious BRCA1/2 and ATM mutations.

For Cohort C, the primary endpoint is confirmed radiologic ORR if measurable visceral and/or nodal disease is present at baseline or ≥ 50% PSA decrease from baseline if visceral and/or nodal disease is absent. For patients with measurable disease, response will be assessed by central IRR.

11.5.2 Secondary Efficacy Analysis

Duration of confirmed response is defined as the time from the date that a response (modified RECIST 1.1 or PSA ≥ 50%) is first reported to the time that progression is first documented:

- For responses per RECIST 1.1, duration of confirmed response is defined as the time from the date that a response (modified RECIST 1.1) is first reported to the time that progression (per modified RECIST Version 1.1 criteria or bone progression per PCWG3) is first documented
- For PSA-response, duration of confirmed response is defined as the time from the date that a response (PSA decrease ≥ 50%) is first reported to the time that PSA progression is first documented

Radiologic PFS (rPFS) is defined as the time from first dose of rucaparib to the date of first objective evidence of radiographic progression (soft tissue or bone lesion) or death due to any cause, whichever occurs first. Radiographic disease progression includes confirmed bone disease progression and soft tissue disease progression adjudicated by independent central radiological review using the PCWG3 guidelines for bone disease and modified RECIST Version 1.1 for soft tissue disease.

OS is defined as the date from first dose of rucaparib to the date of death due to any cause.

Clinical benefit rate (CBR) is defined as the combination of CR, PR, and SD as defined by modified RECIST Version 1.1 and no progression in bone by PCWG3 criteria. Per RECIST, to be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline to lowest post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later. PSA response will be calculated for all patients with PSA values at baseline and at least 1 post-baseline assessment. PSA will be assessed by a local laboratory.

Similarly, PSA response will also be define as ≥ 90% reduction in PSA from baseline to lowest post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later.

Time to PSA progression is defined as the time from first dose of rucaparib to the date that a ≥ 25% increase and absolute increase of ≥ 2 ng/mL above the nadir (or baseline value for patients who did not have a decline in PSA) in PSA was measured. The increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later.

11.5.3 Exploratory Efficacy Analyses

The endpoints for exploratory analyses are:

- To evaluate PRO using the EuroQol 5 dimensions 5 level questionnaire (EQ-5D-5L), Functional Assessment of Cancer Therapy – Prostate (FACT-P), analgesic drug score, and Brief Pain Inventory – Short Form (BPI-SF)
- To assess changes in the molecular profile over time of matched pre- and post-treatment tumor or plasma samples
- To assess concordance in HRR gene mutation status in matched Pre-Screening biopsy tissue, archival primary and metastatic tumor tissue and plasma ctDNA
- To assess ctDNA as a molecular marker of response
- To assess time to first subsequent antineoplastic therapy
- To evaluate loss of heterozygosity (LOH) in metastatic disease site biopsy and archival primary and metastatic tumor tissue samples.
- To evaluate mechanisms of response and resistance in ctDNA and progression tumor tissue samples.

11.5.3.1 Patient-reported Outcome

Patient reported outcome endpoints by FACT-P and BPI-SF will be summarized according to their respective scoring manuals. Analgesic drug score will be recorded according to the World Health Organization (WHO) scale (0 for no medication, 1 for non-opioid pain medication, 2 for opioids for moderate pain, and 3 for opioids for severe pain).

Analyses of change and/or percent change from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D-5L instrument and the EQ VAS. Patients who do not have both a baseline measurement and at least one post-baseline measurement will not be included.

11.5.3.2 Concordance of HRR Gene Status between Metastatic Disease Site Biopsy, Archival Primary and Metastatic Tumor Tissue, and Plasma ctDNA

Pairwise comparisons will be performed for HRR genotyping results between centrally-assessed Pre-Screening biopsy tissue, archival primary and metastatic tumor tissue (where available), and plasma ctDNA in all combinations. In particular, the concordance of genotyping results between archival primary or metastatic tissue and Pre-Screening biopsy tissue will be assessed to explore whether the HRR gene status of the archival primary or metastatic specimen accurately reflects

that found in a Pre-Screening tissue biopsy. Additionally, the sensitivity and specificity of plasma HRR gene assessment relative to the tissue results will be explored.

11.5.3.3 Changes in Tumor Samples and Changes in Circulating Tumor DNA

Changes in the molecular profile over time of matched pairs of pre and post-treatment tumor tissue (if available) and plasma will be evaluated. Additionally, analysis of ctDNA from serially collected blood will be performed to assess early changes in ctDNA that may associate with response to rucaparib, and to identify and characterize the emergence of mechanisms of resistance. The analysis will include but not be limited to reversions in HRR genes that restore wild-type function and mutations in other components of DNA repair and oncogenic signaling pathways.

Plasma and tumor samples may be used for the development of a blood or tissue-based diagnostic test.

Analyses may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some patients (eg, because of very low titer of ctDNA from plasma or low tumor cellularity in tumor samples), or if there are not enough serially collected blood samples from individual patients to allow for adequate biomarker evaluation.

11.5.3.4 Time to First Subsequent Antineoplastic Therapy

Time to first subsequent antineoplastic therapy will be summarized using a Kaplan-Meier plot and descriptive statistics.

11.5.3.5 Loss of Heterozygosity (LOH)

Metastatic disease site biopsy and archival primary and metastatic tumor tissue samples, where available, will be analyzed and assigned a percentage loss of heterozygosity (% LOH) score. The concordance between % LOH in archival primary and metastatic tumor tissue and screening biopsy tissue will be evaluated, and the relationship between %LOH (treated as a binary variable) and response to rucaparib will be explored

11.5.4 Exploratory Pharmacokinetic Analyses

In all patients with at least one PK sample collected, the trough plasma rucaparib PK data (C_{min}) and summary statistics (N, mean, SD, minimum, median, max, CV%) will be reported. The PK data and selected safety and efficacy endpoints will be included in exploratory population PK and exposure-response analyses, and the results will be reported separately.

11.6 Safety Analyses

Safety endpoints include incidence of AEs, clinical laboratory abnormalities, and dose modifications.

Data from all patients who receive at least 1 dose of study drug will be included in the safety analyses. AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

11.6.1 Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE Version 4.03 or later. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until the date of the last study drug dose plus 28 days.

The number and percentage of patients who experienced TEAEs for each system organ class (SOC) and preferred term will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least 1 TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication;
- TEAEs resulting in interruption/delay of study medication; and
- TEAEs resulting in dose reduction of study medication.

The incidence of TEAEs will be summarized by relationship to study drug according to the following categories: “treatment-related,” or “not treatment-related”. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of “Missing.” For each toxicity grade, the number and percentage of patients with at least 1 TEAE of the given grade will be summarized.

11.6.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will generally be presented in SI units. The on-treatment period will be defined as the time from the first dose of study drug to 28 days after

the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum and last value during the on-treatment period.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or 4 criteria according to CTCAE).

11.6.3 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, SD, minimum, median, third quartile, and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, SD, minimum, median and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

11.7 Interim Analysis

Cohort A

As described in Section 11.2, up to approximately 150 patients will be enrolled in Cohort A, which will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort A (BRCA1/2)

A Simon 2-stage design to evaluate confirmed ORR by modified RECIST Version 1.1 criteria per investigator will be used. With rolling enrollment, after the first 37 patients with a deleterious BRCA1/2 mutation have either: a) completed 16 weeks of treatment, or b) discontinued treatment prior to completing, an interim analysis will be performed (ie, Stage 1). If ≤ 8/37 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the DMC will evaluate the overall benefit/risk for patients with deleterious BRCA1/2 mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 9/37 patients have a confirmed objective response, then enrollment will continue with additional patients in Stage 2. With 83 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug

- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

Cohort A (ATM)

A Simon 2-stage type futility rule will be employed in Cohort A (ATM). An interim analysis (Stage 1) will be performed after the first 31 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 6/31 patients in Stage 1 have a confirmed objective response (CR or PR per investigator and without progression in bone per PCWG3), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 7/31 patients have a confirmed objective response, then enrollment will continue in Stage 2. With 53 total patients with a deleterious ATM mutation, characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 35% for an effective drug

Cohort B

As described in Section 11.2, up to approximately 150 patients will be enrolled into Cohort B which will be divided into 2 sub-cohorts defined by deleterious gene mutation (BRCA1/2 vs. ATM).

Cohort B (BRCA1/2)

A Simon 2-stage type futility rule will be employed in Cohort B (BRCA1/2). An interim analysis (Stage 1) will be performed after the first 19 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 4/19 patients in Stage 1 have a PSA response (≥ 50% decrease), the DMC will evaluate the overall benefit/risk for patients with deleterious BRCA1/2 mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 5/19 patients have a PSA response, then enrollment will continue in Stage 2. With 54 total patients with a deleterious BRCA1/2 mutation, characteristics of the Simon 2-stage design include:

- 5% probability of accepting a minimally effective drug
- 90% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 16 responses in 54 patients with a deleterious BRCA1/2 mutation, the null hypothesis (ORR = 20%) will be rejected. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 100 total, may be enrolled. Enrollment in Cohort B (BRCA1/2) will be halted when Cohort A (BRCA1/2) is fully enrolled.

Cohort B (ATM)

A Simon 2-stage type futility rule will be employed in Cohort B (ATM). An interim analysis (Stage 1) will be performed after the first 18 patients have either: a) completed 16 weeks of treatment; or b) discontinued treatment prior to completing. Enrollment into the study will continue while this interim analysis occurs. If ≤ 4/18 patients in Stage 1 have a PSA response (≥ 50% decrease), the DMC will evaluate the overall benefit/risk for patients with deleterious ATM mutations in this cohort and make a recommendation whether further enrollment should be discontinued. If ≥ 5/18 patients have a PSA response, then enrollment will continue in Stage 2. With 33 total patients with a deleterious ATM mutation, characteristics of the Simon 2-stage (minimax) design include:

- 5% probability of accepting a minimally effective drug
- 80% probability of accepting an effective drug
- ORR of 20% for a minimally effective drug
- ORR of 40% for an effective drug

If there are at least 11 responses in 33 patients with a deleterious ATM mutation, the null hypothesis (ORR = 20%) will be rejected. Additionally, if the criteria for Stage 2 are met, additional patients, up to approximately 50 total, may be enrolled. Enrollment in Cohort B (ATM) will be halted when Cohort A (BRCA1/2) is fully enrolled

Cohort C

Up to approximately 60 patients will be enrolled into Cohort C. Enrollment in Cohort C will be halted when Cohort A (BRCA1/2) is fully enrolled. Since this cohort will enroll patients that have 1 of several different deleterious HRR gene mutations, each gene will be examined separately. It is anticipated that < 6 patients will have a deleterious mutation in the same HRR gene; however, if enrollment of patients with a deleterious mutation in the same gene is higher than anticipated then enrollment will be held at 6 patients with any 1 deleterious gene mutation and a futility rule will be implemented such that if no responses are observed, then enrollment of patients with a deleterious mutation in that particular gene will be stopped, in consultation with the DMC.

12 PATIENT DISPOSITION

12.1 Removal of Patients from the Study or Study Drug

A patient must be discontinued from protocol prescribed- therapy if any of the following apply:

- Consent withdrawal for any reason at the patient's own request or at the request of their legally authorized representative;
- Radiographic progression of patient's underlying cancer per modified RECIST Version 1.1/PCWG3 (unless, in the opinion of the investigator, the patient continues to derive clinical benefit; treatment beyond progression is permitted with additional consent);
- Unequivocal clinical progression of the patient's underlying cancer that in the opinion of the investigator requires immediate change in systemic anticancer therapy, or results in marked deterioration in ECOG performance status to Grade 3 or higher
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy;
- Noncompliance by the patient with protocol mandated procedures

Discontinuation of treatment does not necessarily indicate study discontinuation for a patient. Samples collected for research will continue to be used unless the patient explicitly withdraws consent for their use. If the patient withdraws consent to continue in the study or discontinues the study for another reason it will be documented on the appropriate eCRF. A patient may withdraw consent to participate in an additional part of a study that has an additional consent (ie, optional tumor biopsy) yet continue to participate and be treated/ followed in the main part of the study.

The sponsor may discontinue the trial early for any of the reasons noted in Section 13.7.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

13.1.1 Good Clinical Practice

This study will be conducted in accordance with the protocol and applicable standard operating procedures (SOPs); and in compliance with applicable regulations and guidelines including;

- International Council for Harmonisation (ICH) E6 (R2);
- The Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, and 312);
- European Union (EU) Directive 2001/20/EC, 2003/94/EC, 2005/28/EC, 536/2014 and
- All applicable local requirements, and in accordance with the ethical principles of the Declaration of Helsinki.

The investigator will assure that no amendments to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/IEC, and local health authority (where applicable), except where necessary to eliminate an immediate hazard(s) to the study participants.

Significant noncompliance with the protocol, SOPs, Good Clinical Practice (GCP), and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor staff or its representatives will lead to prompt action by the sponsor to secure compliance. If monitoring and/or auditing identifies serious noncompliance on the part of an investigator/institution, the sponsor will take steps to secure compliance or terminate the investigator's/institution's participation in the study. When an investigator's/institution's participation is terminated because of significant noncompliance, the sponsor will promptly notify the regulatory authority(ies) and other appropriate parties (eg, IEC/IRB).

All potential serious breaches of GCP must be reported to the sponsor or designee within 24 hours. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study site personnel where sanctions have been invoked or where there has been scientific misconduct (eg, debarment).

13.1.2 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to applicable regulatory agencies for approval prior to the study start. No patient will begin the study-specific prescreening or screening until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent, when participating in a US Investigational New Drug Application [IND] study). In addition, local statement of investigator documents must be provided where required. Each investigator must submit to the sponsor (or designee) financial disclosure information for studies under US IND or if required by national law and/or local regulations.

The study will be registered on regionally-relevant registries, including www.clinicaltrials.gov, EudraCT, and other applicable clinical study registry systems, as appropriate. Data generated from this study must be handled in accordance with any laws, rules, and regulations related to the privacy of personal data or personal health information applicable in the jurisdiction where the data are processed, including without limitation, the US Health Information Portability and Accountability Act of 1996 (HIPAA), and its implementing regulations, and the EU General Data Protection Regulation 2016/679 (GDPR).

13.1.3 Institutional Review Board or Independent Ethics Committee Approval

This protocol, all protocol amendments, and any material to be provided to the patient (such as the ICF, advertisements, patient information sheets (PIS), or descriptions of the study used to obtain informed consent) must be submitted, reviewed, and approved by the IEC/IRB before study start, according to national law and/or local regulations. There must be proof of submission of the IB to the IEC/IRB. The sponsor will supply relevant information to the investigator to submit the study protocol and additional study documents to the IEC/IRB.

Verification of the IEC's/ IRB's approval of the study protocol and the written informed consent form will be transmitted to the sponsor by the investigator or by other means as determined between the investigator and the sponsor.

No patient will begin the study-specific prescreening or screening until appropriate IEC/IRB approval of the study protocol and ICF/PIS have been received and the investigator has obtained the patient's legally-effective ICF/PIS.

The investigator will submit appropriate reports on the progress of the study to the IEC/IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB.

The IEC/IRB must be informed by the investigator of all SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study, according to institutional policies.

13.2 Patient Information and Consent

13.2.1 General Aspects of Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines, the Declaration of Helsinki, and local requirements.

The ICF(s), prepared by the investigator with the assistance of the sponsor, must comply with all applicable regulations, be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

It is the responsibility of the investigator to obtain legally-effective informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study, answering all questions from the patients regarding the study, and prior to undertaking any study-related procedures.

13.2.2 Informed Consent Process

The patient must be provided with the patient information, if applicable, and the most current IEC/IRB-approved ICF. The investigator or their designee shall discuss with each patient the nature of the study, its requirements, and that participation is voluntary and may be terminated at any time by the investigator or participant. To participate in the study, informed consent must be obtained from each prospective patient prior to any protocol-specific activities.

The ICF must be in a language fully comprehensible to the prospective patient. Patients or legally-authorized representatives (where acceptable according to national law and/or local regulations) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator. The patient and the person conducting the informed consent discussion for the study will personally sign and date the ICF in addition to any other required signature (if applicable). A copy of the signed ICF will be retained by the patient or legally-authorized representative and the original ICF will be filed in the investigator file. The process of obtaining informed consent will be documented in the patient's source documents. The date when a patient's informed consent was obtained will be captured in the patient's source documents and eCRF. The patient will need to re-consent if the ICF is updated during the study, such as after an amendment to the protocol, if mandated by the IEC/IRB.

The patient will have the option to provide additional consent to allow the sponsor to retain residual samples for future unspecified research.

13.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only identification codes (ie, no names or, in some regions, initials or date of birth) according to country regulations will be recorded on any form submitted to the sponsor and the IEC/IRB. The investigator must maintain a list with the identity of all study participants, but not intended for use by the sponsor.

13.4 Study Monitoring

The sponsor, or a contract research organization (CRO) or contract monitor acting on the sponsor's behalf, will contact and visit the investigator at the study center prior to the entry of the first patient (unless the sponsor or the CRO has worked with the center recently, in the same or comparable indication, the site location and facilities have not changed significantly since after

the last visit by the sponsor or CRO, and the potential investigator/site are currently in good standing with respect to regulatory compliance, in which case this initial visit maybe waived) and at predetermined appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, and local regulations, the clinical monitor will periodically review, via direct access, all eCRFs, study documents, medical records (office, clinic, or hospital) for patients in this study (anonymity is to be preserved), research facilities, and clinical laboratory facilities associated with the study at mutually convenient times until completion of the study. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the investigator must inform the sponsor of these restrictions before initiation of the study.

The investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents; however, the investigator retains ultimate responsibility for the quality and integrity of data generated by the site. Aspects of the study that are essential for human patient protection and safety and the reliability of study data shall be confirmed. The investigator will make all source data (ie, the various study records, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) and eCRFs for the entire study period available for the monitor. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification and review).

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file.

13.5 Case Report Forms and Study Data

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner, according to the principles of Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and ‘Plus’ (+) Complete, Consistent, Enduring, and Available (ALCOA+), to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

Prior to study start, the investigator will prepare a list showing the signature, handwritten initials, delegated tasks, and dates of delegations for all individuals delegated responsibility on this study. This “study site personnel and delegation list” must be kept current throughout the study.

Clinical data and clinical laboratory data will be entered into a 21 CFR Part 11-compliant EDC system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. If a patient withdraws from the study, the reason must be noted in the source documents and eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts will be made to clearly document the outcome.

Laboratory data and investigator observations on the results and any other clinically significant test results are to be documented in the source documents and entered into applicable eCRFs.

Full information regarding EDC and completing eCRFs is included in the investigator files. All questions or comments related to EDC should be directed to the assigned monitor.

Clinical data will be entered directly into the eCRFs from the source documents for all participants who are screened.

13.6 Data Monitoring Committee

A DMC will be established to review safety data in compliance with a prospective charter. For Cohort A and B, DMC may be requested to evaluate the overall risk/benefit of rucaparib therapy in this patient population based on the outcome of Stage 1 interim analysis. The DMC will be comprised of study investigators and of sponsor representatives. The DMC responsibilities, authorities, and procedures for this study will be documented in the DMC charter, which will be endorsed by the DMC members and signed by the DMC chair prior to the first data review meeting. The DMC will also ensure the study is beneficial to patients (see Section 11.7).

The DMC will meet after the first 20 patients received rucaparib for at least 28 days or discontinued study treatment, and then at least semi-annually after sufficient data has been collected. The DMC chairperson or sponsor may convene an unscheduled DMC meeting if there are newly identified significant safety concerns. Following data review, the DMC will recommend continuation, revision, or termination of the study and/ or continuing or halting enrollment into a particular subgroup. Details regarding the DMC will be in the committee charter.

13.7 Study Termination and Site Closure

The sponsor, the investigator/institution, or IEC/IRB reserve the right to terminate the study at any time. Should this be necessary, the sponsor and investigator will arrange discontinuation procedures. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

If the trial is terminated prematurely, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The investigators will promptly inform their IRB/IEC, providing the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The sponsor reserves the right to terminate the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study;
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical;
- The stated objectives of the study are achieved; or
- The sponsor discontinues the development of rucaparib.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the source documents and on the eCRF. All reasons for discontinuation of treatment must be documented.

13.8 Study Protocol Amendments

Protocol amendments must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol modifications and changes to the informed consent document. The IEC/ IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities (as required) for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines. Managing protocol deviations is described in Section 13.10.1.

13.9 Retention of Study Documents

The study site will maintain a study file, which will contain all documents defined in the ICH E6(R2) Guideline for Good Clinical Practice. The investigator will have control of all essential documents generated by the site. Source documents must be maintained and ALCOA+ documentation practice used. Any changes to source data will be traceable, will not obscure the original entry, and will be explained if necessary (via an audit trail). The investigator must implement procedures to ensure the integrity of any data generated.

The sponsor and investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version, history, search, and retrieval. The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs, query responses, and detailed records of drug disposition to enable inspections or audits from regulatory authorities, the IEC/IRB, and the sponsor or its designees.

The investigator shall retain records and documents, including signed ICFs, pertaining to the conduct of the study for a period of 25 years after study completion or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents will be retained for a longer period of time if required by the applicable regulatory requirement(s), institutional policies, or if needed by the sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data shall be destroyed without the agreement of the sponsor. Copies of original documents will fulfill the requirements for certified copies. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the trial-related records are no longer needed.

All clinical study information will be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification, irrespective of the media used.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site, but at a minimum, for the period defined by the applicable regulatory requirements.

13.10 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

13.10.1 Protocol Deviations

The investigator may not deviate from the protocol unless necessary to eliminate immediate hazards to the patient. A deviation may result in the subject having to be withdrawn from the study and rendering that patient's data nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor and to the IEC/IRB according to institutional and sponsor requirements.

13.10.2 Study Site Training

Each investigator and the site personnel for this study will be trained by the sponsor and/or a designee (ie, a CRO) on GCP and on the design, conduct, procedures, and administrative aspects of this study. This training may include, but is not limited to, on-site training, Investigator Meeting(s), and/or tele/videoconferencing. Training may be ongoing as refresher, to address specific items, or to introduce changes in the study. When site staff join after study training has been conducted, the investigator is responsible for ensuring that the new staff member is trained.

13.10.3 Quality Assurance Audits and Inspections

An audit of a clinical center may be conducted by a quality assurance auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring

or quality control functions, is to evaluate study conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. IRB/IEC representatives may also conduct an audit of the study at any time.

Representatives of the FDA, European Medicines Agency (EMA), or other regulatory agencies may conduct an inspection of the study at any time. If informed of such an inspection, the investigator will notify the sponsor immediately.

13.10.4 Direct Access to Source Data/Documents for Audits and Inspections

The investigator will ensure that the auditors or inspectors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files and audit trails are available, if requested. It is important that the investigator(s) and their staff cooperate with the quality assurance auditor or regulatory authority inspector during this audit or inspection.

13.11 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the sponsor and signed by the sponsor's Chief Medical Officer, head of biostatistics, and head of regulatory Affairs; thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report. The clinical study report will be provided to the clinical investigator(s) and regulatory agency(ies) as required by the applicable regulatory requirements.

13.12 Publication and Disclosure Policy

All information for the study provided by the sponsor or designee to the investigator, including, but not limited to, the IB, this protocol, eCRFs, the protocol-specified treatment, and any other study information, will remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without the prior written consent of the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

All data generated from this study will be maintained by the sponsor. All data generated from this study, and all information furnished by the sponsor, the investigators, and other participating study groups shall be held in strict confidence. Independent analysis and/or publication of study data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICMJE]).[48] Written permission to the investigator will be contingent on the review of the statistical analysis and manuscript/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 60 days prior to

submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

13.13 Investigator Oversight

The investigator has full responsibility for supervising any individual or party to whom they delegate study-related duties and functions conducted at the study site, including satellite locations. The responsibility for supervision includes the services of any party or individual retained by the investigator for this purpose, regardless of location. All staff delegated study responsibilities must be documented on an approved Delegation of Authority log for the study and this filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by training, experience and licensure (as applicable). The investigator should implement procedures to ensure integrity of the study and data generated.

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15 APPENDICES

Appendix 1 Deleterious HRR Genes Associated with Sensitivity to PARPi

Table 6. Deleterious HRR Genes Associated with Sensitivity to PARPi*

	Prostate Cancer			Ovarian Cancer		*In Vitro* Data	
Gene Symbol	Frequency of deleterious gene mutations observed in mCRPC (%)	Frequency of germline deleterious mutations in mCRPC (%)[c]	Clinical activity of PARPi associated with gene defect[g]	Ovarian cancer susceptibility gene[d]	Clinical activity of PARPi associated with gene defect[h]	References demonstrating *in vitro* sensitivity to PARPi	Reference(s) demonstrating role in HRR
Cohorts A and B							
BRCA1	2.0[b]	0.9	Yes	Yes	Yes[e,f]	Farmer, Nature 2005. Lord, DNA Repair 2008	Moynahan, Mol Cell 1999
BRCA2	13.3[a]	5.3	Yes	Yes	Yes[e,f]	Bryant, Nature 2005. Farmer, Nature 2005. Lord, DNA Repair 2008	Xia, PNAS 2001
ATM	7.3[a]	1.6	Yes	No	Yes[f]	McCabe, Cancer Res 2006. Turner, EMBO 2008. Weston, Blood 2010. Murai, Cancer Res 2012. Shen, CCR 2013	Beucher, EMBO J 2009
Cohort C							
BARD1	NR[a,b,c]	NS	NR	Yes	NS[e], NR[f]	Clovis internal data	Westermark, Mol Cell Biol 2003
BRIP1	0.7[a]	0.2	NR	Yes	Yes[e,f]		Litman, Cancer Cell 2005
CHEK2	4.1[b]	1.9	Yes	No	NS[e], NR[f]	McCabe, Cancer Res 2006	Zhang, Mol Cell Biol 2004
FANCA	6.1[b]	NE	Yes	NE	NS[e], NR[f]	McCabe, Cancer Res 2006	Yang, Carcinogenesis 2005
NBN	2.0[b]	0.3	Yes	No	Yes[e]	McCabe, Cancer Res 2006	Tauchi, Nature 2002
PALB2	2.0[b]	0.4	Yes	Yes	NS[e], NR[f]	Buisson, Nat Struct Mol Biol 2010. Shen, CCR 2013	Buisson, Nat Struct Mol Biol 2010
RAD51	NR[a,b,c]	NE	No	NE	NS[e], NR[f]	McCabe, Cancer Res 2006. Lord, DNA Repair 2008. Shen, CCR 2013	Shinohara, Cell 1992
RAD51B	0.7[a]	NE	NR	NE	NS[e], NR[f]		Takata, Mol Cell Biol 2000
RAD51C	0.7[a]	0.1	NR	Yes	Yes[e]	Min, Mol Cancer Ther 2013	Kurumizaka, PNAS 2001
RAD51D	0.4[c]	0.4	NR	Yes	Yes[e]	Loveday, Nat Genet 2011	Kurumizaka, J Biol Chem 2002
RAD54L	NR[a,b,c]	NE	NR	NE	NS[e], NR[f]	Gottipati, Cancer Res 2010; McCabe, Cancer Res 2006	Sigurdsson, J Biol Chem 2003
~~CDK12~~	~~4.7~~	~~NE~~	~~NR~~	~~NE~~	~~Yes[f]~~	~~Bajrami, Cancer Res 2014. Joshi, J Biol Chem 2014~~	~~Ekumi, Nucleic Acids Res 2015~~

* "deleterious mutation" defined as protein truncating mutations, large protein-truncating rearrangements, splice site mutations, deleterious missense mutations, and homozygous deletions

A total of 15 HRR genes were chosen for evaluation in cohorts A, B and C of this study. Deleterious mutations have been previously reported in mCRPC for most. For those genes where deleterious mutations have not been previously reported or have been reported at low frequency (<1%) in mCRPC, compelling clinical or pre-clinical data referenced here suggests sensitivity to rucaparib, and that patients with these deleterious mutations should not be excluded from the study.

Abbreviations: HRR, homologous recombination repair; mCRPC, metastatic castration-resistance prostate cancer; PARPi, poly ADP ribose polymerase inhibitor; NR, not reported; NS, not seen (this gene was evaluated, but a deleterious mutation or associated clinical activity was not observed); NE, not evaluated

[a] Robinson, Cell 2015
[b] Mateo, N Engl J Med 2015
[c] Pritchard, N Engl J Med 2016
[d] Norquist, JAMA Oncol 2016
[e] Clovis ARIEL2 study data (unpublished)
[f] Lheureux, ASCO Annual Meeting 2016
[g] as reported in Mateo, N Engl J Med 2016; clinical activity is defined as a response by RECIST v1.1; a reduction in prostate-specific antigen (PSA) level of ≥50%; or a conversion in the circulating tumor-cell count from ≥5 per 7.5 ml of blood at baseline to <5 per 7.5 ml during treatment, with a confirmatory assessment ≥4 weeks later
[h] clinical activity is defined as a response by RECIST v1.1 or a reduction in serum CA-125 level of ≥50%
[i] as of 15 February 2018, sufficient CDK12 patients have been enrolled and recruitment has been halted by the DMC, until further notice

Appendix 2 Modified Response Evaluation Criteria in Solid Tumors Criteria (Version 1.1) and Prostate Cancer Working Group 3 Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer et al. 2009[44] and at http://www.eortc.be/Recist/Default.htm. and PCWG3 criteria as described by Scher, et al. 2016[25]

A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- A minimum size of 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

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

Bone Lesions

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria. Bone lesions should not be recorded as target or nontarget lesions to be followed by RECIST 1.1 criteria; this includes bone lesions with a soft tissue component and soft tissue lesions extending from a bone lesion.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ (per PCWG3), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A maximum of 10 target lesions total should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Prostate and prostatic bed lesions should NOT be selected as target lesions, according to PCWG3 criteria.

Nontarget Lesions

RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion. A maximum of 10 target lesions total should be selected.

Guidelines for Evaluation of Measurable Disease

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤ 5 mm contiguous reconstruction algorithm. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements.

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

Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumor lesions.

Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s).
Progressive Disease	Appearance of 1 or more new extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Evaluation of Best Overall Response

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

Evaluation of Best Overall Response: Patients with Target (+/- Non-Target) Disease			
Target Lesions	**Nontarget Lesions**	**New Lesions[a]**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] New bone metastatic lesions should not be considered as a 'Yes' response; only new extra-skeletal lesions.

Evaluation of Best Overall Response: Patients with NonTarget- Disease Only		
Nontarget Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmation

If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later.

Duration of Response

CT scans are required for this study at screening and every 8 calendar weeks (within 7 days before or after is permitted) thereafter. Patients who have been on study at least 24 weeks, may decrease the frequency of disease/ tumor assessments to every 12 calendar weeks (within 7 days before or after is permitted).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started), including progression in bone per PCWG3 criteria.

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

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

PCWG3 Criteria for Assessment of Bone Disease

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016[25]

Imaging of Baseline Bone Disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-MDP or HDP radionuclide bone scintigraphy
- Confirm ambiguous results by other imaging modalities (eg, CT or MRI) however only positivity on the bone scan defines metastatic disease to bone

Documentation of baseline bone disease

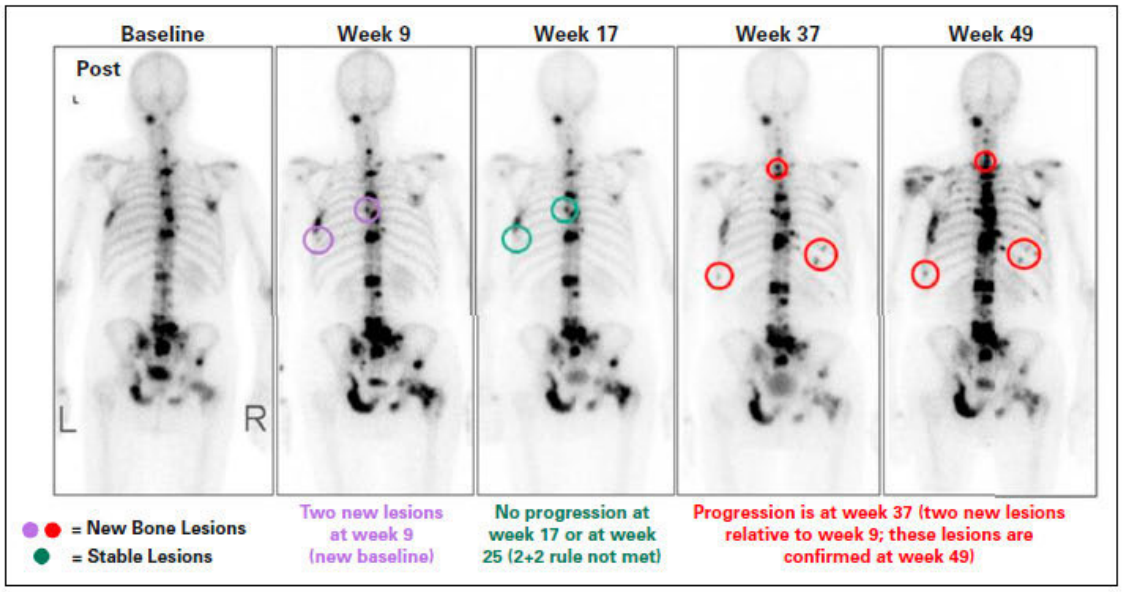
- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial

Following for bone progression during the study

- Exclude pseudoprogression in the absence of symptoms or other signs of progression

- At least two new lesions on scans during the 12-week flare window (ie, the first post-treatment scan), which are persistent and appear with at least two additional lesions on the next scan after the 12-week flare window (2+2 rule)
- If at least two additional new lesions are seen on the next (confirmatory) scan performed after the 12-week flare window, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
- For scans after the 12-week flare window (ie, after the first post-treatment scan), at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
- Date of progression is the date of the scan that first documents the second lesion
- Changes in intensity of uptake alone do not constitute either progression or regression

Figure 3. Controlling for Flare by Applying the 2+2 Rule using the First Post-treatment Scan as Baseline



PCWG3 Criteria for Confirmation of Radiographic Progression in Bone by Investigator Assessment (to be used in conjunction with modified RECIST 1.1 criteria for visceral and nodal disease)

Date Progression Detected (Visit)	**Criteria for Progression in Bone**	**Criteria for Confirmation of Progression in Bone**
Week 9 (1st on-treatment scan)	Two or more new lesions on bone scan compared to **baseline** bone scan by PCWG3	Two or more new bone lesions identified at Week 9 must persist at Week 17 and 2 or more additional new lesions must be identified on Week 17 bone scan (compared to Week 9 scan)
Week 17 (2nd on-treatment scan)	Two or more new lesions on bone scan compared to **Week 9** bone scan.	Two or more new lesions identified at Week 17 must persist at Week 25 bone scan
Week 25 and after (3rd on-treatment scan and after)	Two or more new lesions bone scan compared to **Week 9** bone scan	Two or more new lesions identified at Week 25 (or later) bone scan must persist at scan obtained 6 weeks later

Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

In the event performance status is assessed by the Karnofsky Performance Status scale, the following conversion chart applies.

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

Appendix 4 Cockcroft-Gault Formula

Estimated Glomerular Filtration Rate

Estimated GFR using serum creatinine value is at Screening and each time clinical chemistry testing occurs.

$$\text{Male } CL_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}$$

$$\text{Female } CL_{cr} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}\right] \times 0.85$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL; the calculated units are mL/min.

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times \textit{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

Appendix 5 Examples of CYP Substrates with Narrow Therapeutic Range

Table 7. Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range[a]
CYP1A2	Tizanidine, theophylline
CYP2C9	Warfarin, phenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

[a] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

Online reference tool:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm

Source: Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012.[49]

Appendix 6 Brief Pain Inventory - Short Form (BPI-SF)

A sample form for the BPI-SF is below and background for the questionnaire is available at https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html.

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

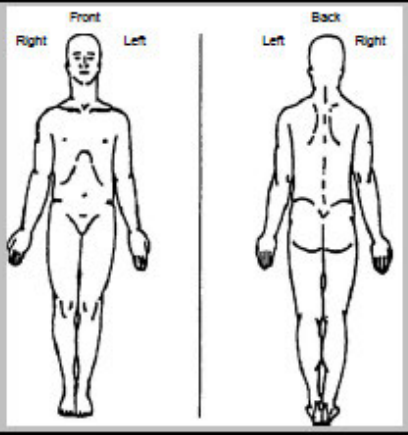
Date: ____/____/____ **Time:** _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____

Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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Appendix 7 Functional Assessment of Cancer Therapy - Prostate (FACT-P)

A sample form for the FACT-P is below and background for the questionnaire is available at http://www.facit.org/facitorg/questionnaires.

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

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix 8 Euro-Quality of Life 5D 5L (EQ-5D-5L) Patient Reported Outcome

A sample form for the EQ-5D-5L is included on the next page. Background information for the questionnaire is available at http://www.euroqol.org/home.html.

Health Questionnaire

English version for the USA

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

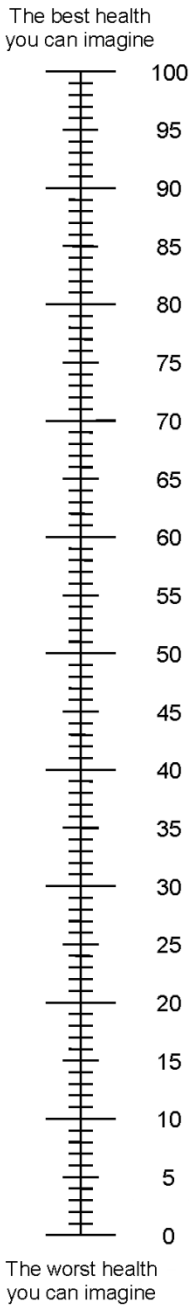
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 9 Analgesic Use Questionnaire

A sample form for the Analgesic Use Questionnaire is included on the next page.

Study ID #	CO-338-052 (TRITON2)	**Site No**	
Patient ID:	**52-** _____-_____	**Date**	

Analgesic Use Questionnaire

Please indicate the strongest pain medication you have taken within the past 24 hours:

☐ 0 = No pain medication

☐ 1 = Non-opioid pain medication such as aspirin [salicylate], acetaminophen [paracetamol], other non-steroidal anti-inflammatory drug [NSAID], etc.

☐ 2 = Mild opioid pain medication such as codeine, hydrocodone, tramadol, etc.

☐ 3 = Strong opioid pain medication such as morphine, oxycodone, hydromorphone, fentanyl, methadone, etc.

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