**ClinicalTrials.gov Official Title:** Study of Oral Rucaparib with Other Anticancer Agents in Metastatic Castration Resistant Prostate Cancer Patients (RAMP)

**ClinicalTrials.gov Identifier Number:** NCT04179396

**Document Date:** 19 January 2022

**Document:** Clinical Study Protocol CO-338-107

**Study Title:** RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other

# CLINICAL STUDY PROTOCOL: CO-338-107

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|---|---|
| **Study Title:** | RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration-Resistant **P**rostate Cancer |
| **Study Number:** | CO-338-107 |
| **Study Phase:** | Phase 1b |
| **Product Name:** | Rucaparib (CO-338) |
| **IND 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** |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| Amendment 2: | 19 January 2022 |

**Confidentiality Statement**

# PROTOCOL APPROVAL SIGNATURE PAGE

**Protocol:** CO-338-107

**Title:** RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration Resistant **P**rostate Cancer

**Date:** 19 January 2022

**Version:** Amendment 2

# PROTOCOL ACCEPTANCE FORM

**Protocol:** CO-338-107

**Title:** RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration Resistant **P**rostate Cancer

**Date:** 19 January 2022

**Version:** Amendment 2

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 MMM YYYY) |
|---|---|

Name (printed)

# SPONSOR'S MEDICAL EXPERT FOR THE STUDY

**Medical Expert:**

# PROTOCOL SYNOPSIS

**Sponsor:**
Clovis Oncology, Inc.

**Name of Finished Product:**
Rucaparib tablets
Enzalutamide capsules
Abiraterone tablets

**Name of Active Ingredient:**
Rucaparib camsylate (CO-338)
Enzalutamide
Abiraterone acetate

**Study Title:**
RAMP: A Phase 1b, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral **R**ucaparib in Combination with Other **A**nticancer Agents in Patients with **M**etastatic Castration Resistant **P**rostate Cancer

**Study Number:**
CO-338-107

**Study Phase:**
Phase 1b

**Study Duration:**
Q4 2019-Q4 2022

**Background and Study Rationale:**
Prostate cancer is the most common malignancy among men in the United States (US), and the second-most common cause of cancer-related mortality, with approximately 30,000 men dying of the disease each year.[1] Based upon GLOBOCAN 2018 estimates, prostate cancer is the second leading malignancy diagnosed and the fifth leading cause of death from cancer in men worldwide, with almost 359,000 deaths estimated in 2018.[2] 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 therapy 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 breast cancer gene 2 (BRCA2) are at increased risk for developing prostate cancer, estimated at 2.5 to 8.6-fold compared with non-carriers.[3] 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 breast cancer gene 1 (BRCA1) are also associated with more aggressive disease.[4] In addition to germline mutations in breast cancer gene 1 or 2 (BRCA1/2), somatic mutations in BRCA1/2 and

other homologous recombination deoxyribonucleic acid (DNA)-repair 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 homologous recombination repair (HRR), such as a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor (PARPi).[5]

The TRITON2 study (CO-338-052) is evaluating rucaparib in patients with DNA-damage repair (DDR) gene alterations who progressed on 1 to 2 lines of androgen receptor (AR)-directed therapy and 1 prior line of taxane-based chemotherapy for mCRPC. Interim efficacy results from the TRITON2 study in breast cancer gene (BRCA)-mutated mCRPC patients administered rucaparib 600 mg twice a day (BID) demonstrated a 44% overall response rate (ORR) by independent radiology review (IRR) in 62 patients evaluable by Response Evaluation Criteria in Solid Tumors (RECIST Version [v]1.1) modified according to Prostate Cancer Working Group Guidelines Version 3 (PCWG3), combined with evaluation of bone disease according to PCWG3 (mRECIST/PCWG3).[6] Clinical activity was also observed in patients with other DDR gene alterations. In addition, the PARPi olaparib and niraparib have shown evidence of clinical activity in mCRPC patients with a DDR alteration.[7, 8] These findings provide compelling evidence for use of a PARPi in a selected population of mCRPC patients with predicted loss-of-function alterations in a DDR gene, including BRCA1/2.

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 AR pathway, abiraterone acetate and enzalutamide.[9-13] Based on their tolerability and proven efficacy in the prechemotherapy setting, abiraterone acetate and enzalutamide are often used as first-line therapies for mCRPC; however, patients progress on these AR-directed therapies after a median duration of 16 to 18 months on treatment.

Recent studies have demonstrated complex cross-talk between ARs and the DDR pathway. The bulk of evidence suggests regulation of double-strand break (DSB) repair by the AR;[14-17] therefore, AR antagonists used in prostate cancer treatment cause irreparable DSBs and point to a viable synergy between AR-directed therapies and PARP inhibitors, independent of homologous recombination gene mutations.[14] This hypothesis has been clinically tested in a randomized study where the combination of olaparib and abiraterone in unselected mCRPC patients was found to be superior to the abiraterone alone arm with a hazard ratio (HR) of 0.65 (median radiographic progression-free survival [rPFS] 13.8 vs. 8.2 months).[18]

Novel therapies that provide robust clinical benefit and have a manageable safety profile are still needed for patients with advanced mCRPC. Therefore, evaluation of rucaparib in combination with other anticancer therapies, such as an AR antagonist or other therapeutic option, represents a viable treatment option for patients with and without evidence of HRD.

The study will evaluate the combinations of rucaparib with 2 widely used AR-directed therapies, enzalutamide and abiraterone. Enzalutamide is a next-generation anti-androgen

that acts on multiple steps of AR signaling within prostate cancer tumor cells and is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC).[19, 20] Abiraterone is an inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), an enzyme expressed in testicular, adrenal and prostatic tumor tissues, which is required for androgen biosynthesis. The blockade of nongonadal androgen production is a key factor in treating CRPC, since prostate cancer cells are dependent on androgens. Abiraterone is indicated in combination with prednisone for the treatment of patients with mCRPC and metastatic high-risk castration-sensitive prostate cancer (CSPC).[21] The addition of prednisone is to prevent mineralocorticoid excess-related adverse events (AEs; such as hypertension, hypokalemia and fluid retention), resulting from CYP17 inhibition.[22]

Subsequent arms of the study may include other combination partners (eg, other AR-directed therapy in development or immune modulators such as checkpoint inhibitors).

**Study Arms**

**Treatment Arm A:** Rucaparib and enzalutamide

**Treatment Arm B:** Rucaparib and abiraterone

**Primary Objective:**

- To evaluate the pharmacokinetics (PK), safety and tolerability of rucaparib in combination with other anticancer agents for mCRPC.

**Secondary Objectives:**

- To evaluate the preliminary efficacy of rucaparib in combination with other anticancer agents for mCRPC.

**Exploratory Objectives:**

- To evaluate the PK of mCRPC anticancer agents when administered in combination with rucaparib.
- To assess the relationship between genomic alterations detected in tissue or blood with clinical outcomes to treatment.
- To assess the relationship between changes in circulating tumor DNA (ctDNA) profiles over time and clinical outcomes to treatment.

**Study Design:**

This is a Phase 1b, open-label study with multiple treatment arms evaluating the PK, safety, tolerability and preliminary efficacy of rucaparib in combination with other anticancer therapies in patients with mCRPC. The study is designed to test the combination of rucaparib with AR-directed therapy (enzalutamide [Arm A] and abiraterone [Arm B]). Each arm consists of an initial PK, safety and tolerability assessment. Once completed, additional patients may be evaluated to better characterize the PK, safety/tolerability and preliminary efficacy of the combination in an expansion phase.

Patients participating in this study will enroll into one of the study arms (in either the PK assessment phase or the expansion phase). If a patient appears to be eligible for more than one treatment arm that is open to enrollment, the investigator will be responsible for selecting the most appropriate treatment arm for the patient. However, enrollment into Arm A will be prioritized over Arm B until the objectives for Arm A have been achieved.

A run-in period of 1 week of rucaparib monotherapy has been included in the study design, following which, the combination of drugs will be administered. The run-in period is designed to assess the PK of rucaparib administered as monotherapy, prior to any administration of the combination drug, as this may impact the PK of rucaparib. This run-in period will occur both in the initial PK phase as well as the expansion phase of the study.

All dose levels of Arm A (enzalutamide combination) will use the approved dose of 160 mg once a day (QD) enzalutamide; similarly, all dose levels of Arm B (abiraterone combination) will use the approved dose of 1,000 mg QD abiraterone along with 5 mg BID prednisone.

- In Arm A, based on the individual safety profiles of both rucaparib and enzalutamide, no significant overlap in toxicity is expected. Therefore, the approved monotherapy dose of each agent will be the starting dose for the initial combination evaluation. Patients will be closely monitored for safety and tolerability and the dose of rucaparib may be reduced, if appropriate, based on emerging safety data. Preliminary assessment of the metabolic profile of rucaparib and enzalutamide indicates that rucaparib exposure may be diminished due to cytochrome P450 (CYP)3A4 induction by enzalutamide. Therefore, depending on the PK profile of rucaparib, and taking into account the emerging safety/tolerability data, the rucaparib dose may be escalated beyond the starting dose of 600 mg BID. Rucaparib escalation, up to a maximum dose of 1,000 mg BID rucaparib, may be explored based on emerging PK, safety and tolerability data. The increase in rucaparib dose will be determined by exposure observed in the prior cohort of patients.
- In Arm B, the target combination doses will be the approved monotherapy doses for abiraterone and rucaparib. It is not anticipated that abiraterone will reduce rucaparib exposure. However, the dose of rucaparib may also be increased beyond 600 mg BID if there is unexpected lower exposure with co-administration of abiraterone, similar to the approach outlined for Arm A. However, as there is potential for overlapping toxicities with this combination, the initial starting dose for rucaparib will be 400 mg BID, with escalation planned to 600 mg BID if the initial dose level is deemed safe and tolerable. If a dose of 600 mg BID rucaparib in combination with the standard dose of abiraterone is not tolerated, a dose of 500 mg BID rucaparib in combination with the standard dose of abiraterone may be explored.

Up to 3 dose levels may be tested in the initial PK and safety/tolerability assessment phase, with a maximum of 6 patients in each dose level. Further assessment of PK, safety/tolerability and preliminary efficacy of the combination may be made in an expansion phase, enrolling up to 12 patients per arm.

Screening assessments will include demographics and medical history, prior treatments, prior and current medications and procedures, 12-lead electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status, hematology, laboratory chemistry, urinalysis, a baseline disease/tumor assessment by computed tomography (CT)/magnetic resonance imaging (MRI)/bone scan, PSA measurement, physical examination, height, weight, and vital signs measurements and AE assessment. Archival tumor tissue, and preferably optional screening biopsies, will be collected, if available.

Samples for ctDNA and germline testing will be collected for exploratory assessments during the PK run-in period. PK collection for both arms is performed following a 1-week run-in period with rucaparib alone. PK of rucaparib in combination with enzalutamide in Arm A will be assessed over 2 cycles (one cycle is 28 days) due to the longer half-life of enzalutamide and its metabolites, while PK of rucaparib in combination with abiraterone will be assessed over a single cycle (also 28 days) in Arm B. Samples collected for longitudinal ctDNA profiling and pharmacogenomics will be analyzed to evaluate gene variants associated with the clinical activity and PK of the study drugs.

As of the implementation of Protocol Amendment 2, during and at the end of treatment, patients will undergo a more limited number of assessments; however, an appropriate level of safety monitoring will remain in place. Patients will be monitored for AEs, but only serious adverse events (SAEs) and adverse events of special interest (AESIs) will be reported through 28 days after last dose of study drug. Hematology assessments are advised on a monthly basis, and vital signs, clinical chemistry, and urinalysis assessments will be performed according to local standard of care per investigator.

Disease/tumor assessments and PSA measurements will be performed according to local standard of care per investigator.

The End-of-Treatment (EOT) Visit and the 28-day safety Follow-up Visit will include an assessment of AEs. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization. After the 28-day Follow-up Visit, only SAEs assessed as potentially related to study drug should be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database.

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 similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28 days after the last dose of study drug). After the 28-day Follow-up Visit, only **serious** pneumonitis or similar events assessed as **potentially related to study drug** should be reported per Clovis Oncology PV requirements.

Any drug modifications (treatment interruption, dose modifications, and/or treatment discontinuation) will be documented in the electronic Case Report Form (eCRF) and source documents, until the implementation of Protocol Amendment 2, after which it is no longer required to collect data in the eCRF. If a patient has radiologic progression, but continues to derive clinical benefit per the investigator, then continuation of treatment with the combination 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.

**Number of Patients:**

The total enrollment planned for this study is approximately 12 to 60 patients. Each arm of the study will enroll as follows:

PK assessment phase: 6 to 18 patients

Expansion phase: Up to 12 patients

**Number of Sites:**

Patients will be enrolled across up to 10 sites in the US.

**Inclusion Criteria:**

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criterial apply to patients enrolling into all parts of the study:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form prior to any study-specific evaluation.
2. Be ≥ 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).
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) agonists (ie, patients who have not undergone an orchiectomy), therapy must be continued throughout the study.
5. Be either AR-directed therapy naïve or have received 1-2 lines of AR-directed therapy in the castration-resistant setting. If most recently treated with enzalutamide in the castrate-resistant setting, patients must have had no enzalutamide treatment for at least 6 weeks prior to prior to the first planned dose of rucaparib. If most recently treated with an AR-directed therapy other than enzalutamide, patients must have ceased AR-directed therapy treatment for at least 4 weeks prior to prior to the first planned dose of rucaparib.
6. Have disease progression after initiation of most recent therapy 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 mRECIST.
   c. Radionuclide bone scan: at least 2 new metastatic lesions.
7. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to enrollment:
   a. Bone Marrow Function
      i. Absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L;
      ii. Platelets ≥ $100 \times 10^9$/L;

iii. Hemoglobin ≥ 10 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment. Transfusions are not permitted between the screening hemoglobin assessment and the first dose of rucaparib.

b. Hepatic Function

i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN;

ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome;

iii. Serum albumin ≥ 30 g/L (3.0 g/dL).

c. Renal function

i. Serum creatinine ≤ 1.5 × ULN; OR

ii. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft-Gault formula.

8. Have an ECOG performance status of 0 to 1 within 14 days prior to the first dose of rucaparib.
9. Have a life expectancy of at least 6 months.
10. Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection may be enrolled if they have undetectable viral load with antiviral medication and if the antiviral medications do not interfere with any of the study drugs.

**Exclusion Criteria:**

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

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which he may be (but not necessarily) currently receiving treatment. Exceptions are patients with history of malignancy that has been successfully treated, with no evidence of active cancer for 3 years prior to enrollment, or surgically cured and/or low risk tumors, such as non-melanoma skin cancers.
2. Have received greater than 2 previous lines of chemotherapy for mCRPC, including taxanes.
3. Prior treatment with any PARP inhibitor.
4. Spinal cord compression, symptomatic and/or untreated central nervous system (CNS) metastases or leptomeningeal disease. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
5. Severe concurrent disease, infection, comorbidities.
6. Known hepatic disorder that would affect drug metabolism or gastrointestinal disorders that would potentially alter absorption.
7. Any clinically significant cardiovascular disease.
8. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with ingestion or absorption of rucaparib or the combination treatment.

9. Received anticancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs (other than gonadotropin releasing hormone [GnRH] therapy or approved bone-targeting agents) ≤ 14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology of Criteria for Adverse Events (CTCAE) Version 5.0 (v5) Grade 1, with the exception for alopecia and Grade 2 peripheral neuropathy.
10. Nonstudy related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration.
11. Taking any concomitant medications or herbs that could confound PK assessment.
12. 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 ineligible for entry into the study.
13. Refusal to undertake the following measures for the duration of the study and after the last dose of study drug for the time period specified:
    a. Using a condom during sex while being treated and for 3 months after the last dose of study drug,
    b. Abstaining from semen donations during treatment and for 3 months after the last dose of rucaparib.
14. Those with female partners of childbearing potential will be excluded if they are not:
    a. Documented to be surgically sterile (ie, vasectomy); or
    b. Committed to practicing true abstinence during treatment and for 3 months after the last dose of study drug; or
    c. Committed to using a highly effective method of contraception with their partner during treatment and for 3 months following the last dose of study drug.
15. Cohort-specific exclusion criteria:
    a. Arm A: Patients with
        i. A history of seizures or traumatic brain or head injury, and/or receiving concomitant medication that lowers seizure thresholds; or
        ii. Uncontrolled or suboptimally controlled ischemic heart disease, history of myocardial infarction/unstable angina, coronary vascular intervention such as percutaneous coronary intervention (PCI), stent placement or coronary artery bypass graft (CABG) within past 1 year, stable angina or New York Heart Association (NYHA) Class 2 to 4 heart failure.
    b. Arm B: Patients with:
        i. Mean resting QTc > 470 msec obtained from 3 consecutive ECGs;
        ii. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third degree heart block, etc.;

iii. Any history of syncope of suspected/confirmed cardiovascular etiology, ventricular arrhythmia of pathologic origin, uncontrolled atrial fibrillation, or sudden cardiac arrest within the past 1 year;

iv. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age, or any concomitant medication known to prolong the QT interval;

v. History of hypokalemia < 3 mmol/L, uncontrolled hypertension (defined as median BP ≥ 160/90 mm Hg on three serial measurements performed at the time of screening despite maximal medical management) or presence of symptoms due to elevated blood pressure at the time of screening;

vi. Grade 2 edema of any kind (generalized, pitting, or peripheral); or

vii. Diagnosis of Addison's disease.

**Randomization:**

No randomization or blinding will be performed in the study.

**Study Treatment:**

Patients will take the dose of rucaparib they are assigned, orally BID, as close to 12 hours apart as possible and preferably at the same times every day, with approximately 8 oz (240 mL) of water starting on Day 1. Rucaparib tablets must be swallowed whole and may be taken with or without food. Rucaparib will be provided as 200 mg, 250 mg, and/or 300 mg dose strength tablets.

Patients will take rucaparib BID for continuous 28-day cycles until disease progression as assessed by the investigator, or other reason for discontinuation. Dose modification is permitted in the event of unacceptable toxicity.

In Arm A (enzalutamide), patients will take 160 mg once daily, with or without food. Patients who have not had a bilateral orchiectomy should continue the GnRH analog they were taking prior to enrolling into this study.

In Arm B (abiraterone), patients will take 1,000 mg orally QD with prednisone 5 mg orally BID. Abiraterone must be taken on an empty stomach with water at least 1 hour before or 2 hours after a meal, without crushing or chewing tablets. Patients who have not had a bilateral orchiectomy should continue the GnRH analog they were taking prior to enrolling into this study.

Dose reductions will not be permitted for enzalutamide, abiraterone or prednisone during the PK assessment phase, unless the patient experiences a dose-limiting toxicity (DLT). Dose reduction of enzalutamide, abiraterone or prednisone will be allowed for patients who were enrolled in the PK assessment phase portion of the study and have completed the required treatment period for assessment of DLT or who are enrolled in the dose expansion phase, as per the relevant prescribing information.

**Withdrawal Criteria:**

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

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative (where acceptable according to national law and/or local regulations).
- Progression of patient's underlying disease by mRECIST/PCWG3 criteria as assessed by the investigator (unless, in the opinion of the investigator, the patient continues to receive clinical benefit).
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient. If it is determined that 1 of the study drugs in the combination is posing a safety risk and that study drug is permanently discontinued, administration of the other study drug may continue if none of the other withdrawal criteria have been met and the investigator believes that the patient may continue to receive benefit.
- Any concomitant 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; or
- The study is terminated.

**Efficacy Assessments:**

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

Disease/tumor assessments will be performed according to local standard of care per investigator, until confirmed radiologic disease progression by mRECIST criteria, as assessed by the investigator, loss to follow-up, withdrawal, or study closure.

Prostate-specific antigen (PSA) levels will be collected according to local standard of care per investigator, and as clinically indicated.

**Safety Assessments:**

Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, severity, and causality of AEs reported (CTCAE v5.0 or later);
- 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.

As of the implementation of Protocol Amendment 2, during and at the end of treatment, patients will undergo a more limited number of assessments. Adverse events will be monitored, but only SAEs/AESIs will be reported through 28 days after the last dose of study drug.

Hematology assessments (complete blood count) are advised on a monthly basis. Clinical chemistry, urinalysis, and vital sign assessments will be performed according to local standard of care per investigator.

**Pharmacokinetic Assessments:**

Sparse predose PK sampling for rucaparib and/or its combination partner will be performed on Run-In Days 6 and 7 of the 7-day rucaparib run-in treatment, and predose on Days 1, 8, 15 and 22 of Cycle 1 and Day 1 of subsequent cycles in all patients. In addition, in Arm A, sparse predose PK samples will be collected on Days 8, 15 and 22 of Cycle 2. Potential drug-drug interactions (DDIs; effect of combination partner on rucaparib PK) will be assessed based on PK data in Cycles 1 and 2 for Arm A and Cycle 1 for Arm B.

The PK and DDI assessments have been completed and no additional samples will be collected for analysis.

**Statistical Methods:**

**Sample Size**

In each study arm, 6 to 18 patients (up to 3 dose cohorts) will be enrolled in the PK assessment phase; and up to 12 patients will be enrolled in the expansion phase.

**Safety Analyses**

All safety analyses will be summarized for the Safety Population separately for each treatment arm. Within a treatment arm, safety analyses will be summarized by dose cohort (if applicable) and pooled for all patients in the PK/dose-finding cohort and in the expansion cohort.

Adverse events, 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 NCI CTCAE v5.0 or later. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized categorically.

**Efficacy Analysis:**

Confirmed ORR is defined as the proportion of patients with a documented and confirmed best overall response of complete response (CR) or partial response (PR) as assessed by the investigator using mRECIST/PCWG3 criteria. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment no less than 4 weeks after initial response. ORR (confirmed CR + PR) will also be summarized with frequencies and percentages. Changes in PSA levels will also be summarized. The frequency and percentages of patients with a best overall response of CR, PR, stable disease (SD), or progressive disease (PD) will be summarized. All summaries of response rate will be accompanied by 95% confidence intervals (CIs).

**Pharmacokinetic Analyses**

Sparse blood sampling for PK analyses of both rucaparib and the combination drug partner will be conducted in all patients. The PK parameters will be determined using non-compartmental methods and will be reported. Predose concentrations (ie, minimum concentration during a dose interval [$C_{min}$]) of rucaparib, combination drug partners, and metabolites of interest (if any) will be reported. The effect of combination drug on the PK of rucaparib and its metabolite, M324, will be assessed by comparing their steady-state $C_{min}$ with and without treatment of the combination drug in each arm. The M324-to-rucaparib steady-state $C_{min}$ ratio with and without treatment of the combination drug in each arm will also be determined.

**Dose Cohort Review Committee:**

This committee will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites. Prior to initiating treatment at each new dose level or prior to expanding a dose level, the committee will review patient data, including, but not limited to, demographics, PK results, study drug dosing, concomitant medications, hematology and serum chemistry, and AEs. The discussion and agreement to escalate or reduce the rucaparib dose and/or expand an existing dose level will be documented.

**Date of Protocol Approval (Amendment 2):**

19 January 2022

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| ADME | absorption, distribution, metabolism and excretion |
| ADP | adenosine diphosphate |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALCOA+ | attributable, legible, contemporaneous, original or certified copy, accurate, and plus (+) complete, consistent, enduring, and available |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| AR | androgen receptor |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{0-24}$ | area under the concentration-time curve from 0 to 24 hours |
| $AUC_{0-inf}$ | area under the concentration-time curve from 0 to infinity |
| BCRP | breast cancer resistance protein |
| BER | base excision repair |
| BID | twice a day |
| BRCA | breast cancer gene |
| BRCA1 | breast cancer gene 1 |
| BRCA2 | breast cancer gene 2 |
| BRCA1/2 | breast cancer gene 1 or 2 |
| BUN | blood urea nitrogen |
| $C_{max}$ | maximum concentration |
| $C_{min}$ | minimum concentration during a dose interval |
| $C_{trough}$ | concentration before the next dose is administered |
| CABG | coronary artery bypass graft |
| CFR | Code of Federal Regulations |
| CI | confidence interval |

| | |
|---|---|
| CL/F | apparent clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| CNS | central nervous system |
| CR | complete response |
| CrCL | creatinine clearance |
| CRO | contract research organization |
| CRPC | castration-resistant prostate cancer |
| CSPC | castration-sensitive prostate cancer |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | circulating tumor DNA |
| CYP | cytochrome P450 |
| CYP17 | 17α hydroxylase/C17,20-lyase |
| DDI | drug-drug interaction |
| DDR | DNA damage repair |
| DILI | drug-induced liver injury |
| DLT | dose-limiting toxicities |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| DSB | double-strand break |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EOC | epithelial ovarian cancer |
| EOT | End-of-Treatment |
| EU | European Union |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed paraffin-embedded |
| FSH | follicle-stimulating hormone |

| | |
|---|---|
| FTC | fallopian tube cancer |
| GCP | Good Clinical Practice |
| GCSF | granulocyte-colony stimulating factor |
| GDPR | General Data Protection Regulation |
| GFR | glomerular filtration rate |
| GnRH | gonadotropin releasing hormone |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HDPE | high-density polyethylene |
| HIV | human immunodeficiency virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HPLC | high-performance liquid chromatography |
| HR | hazard ratio |
| HRD | homologous recombination deficiency |
| HRR | homologous recombination repair |
| IB | Investigator's Brochure |
| 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 radiology review |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IV | intravenous |
| IWRS | Interactive Web Response System |
| LD | longest diameter |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein |

| | |
|---|---|
| LFT | liver function test |
| LHRH | luteinizing hormone-releasing hormone |
| LOH | loss of heterozygosity |
| MATE | multidrug and toxin extrusion transporter |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| mCRPC | metastatic castration-resistant prostate cancer |
| MCV | mean corpuscular volume |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRECIST | Modified RECIST version 1.1 |
| mRECIST/ PCWG3 | Response Evaluation Criteria in Solid Tumors modified according to PCWG3 guidelines, combined with evaluation of bone disease according to PCWG3 |
| MRI | magnetic resonance imaging |
| MS | mass spectrometry |
| N/A | not applicable |
| NCI | National Cancer Institute |
| NGS | next-generation sequencing |
| NYHA | New York Heart Association |
| OAT | organic anion transporter |
| OCT | organic cation transporter |
| ORR | overall response rate |
| PARP | poly(ADP-ribose) polymerase |
| PARPi | poly(ADP-ribose) polymerase inhibitor |
| PCI | percutaneous coronary intervention |
| PCWG3 | Prostate Cancer Working Group Guidelines Version 3 |
| PD | progressive disease |
| PET | positron emission tomography |
| P-gp | P-glycoprotein |
| PIS | Patient Information Sheet |
| PK | pharmacokinetic |
| PPC | primary peritoneal cancer |

| | |
|---|---|
| PPI | proton pump inhibitor |
| PPK | population pharmacokinetics |
| PR | partial response |
| PRES | posterior reversible encephalopathy syndrome |
| PSA | prostate-specific antigen |
| PT | Preferred Term |
| PV | pharmacovigilance |
| QD | once a day |
| QTc | QT interval corrected for heart rate |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| rPFS | radiographic progression-free survival |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SI | International System of Units |
| StD | standard deviation |
| SOA | schedule of assessments |
| SOC | system organ class |
| SOP | standard operating procedure |
| SmPC | Summary of Product Characteristics |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2}$ | half-life |
| $t_{max}$ | time to maximum concentration |
| TEAE | treatment-emergent adverse events |
| UGT | uridine diphosphate-glucuronosyl transferase |
| ULN | upper limit of normal |
| US | United States |
| V | version |
| WBC | white blood cell |

# 1 INTRODUCTION

## 1.1 Background

Prostate cancer is the most common malignancy among men in the United States (US), and the second-most common cause of cancer-related mortality, with approximately 30,000 men dying of the disease each year.[1] Based upon GLOBOCAN 2018 estimates, prostate cancer is the second leading malignancy diagnosed and the fifth leading cause of death from cancer in men worldwide, with almost 359,000 deaths estimated in 2018.[2] 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 therapy 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 breast cancer gene 2 (BRCA2[1]) are at increased risk for developing prostate cancer, estimated at 2.5 to 8.6-fold compared with non-carriers.[3] 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 breast cancer gene 1 (BRCA1) are also associated with more aggressive disease.[4] In addition to germline mutations in BRCA1/2, somatic mutations in breast cancer gene 1 or 2 (BRCA1/2) and other homologous recombination deoxyribonucleic (DNA)-repair 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 homologous recombination repair (HRR), such as a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor (PARPi)[5]

The TRITON2 study (CO-338-052) is evaluating rucaparib in patients with DNA damage repair (DDR) gene alterations who progressed on 1 to 2 lines of androgen receptor (AR)-directed therapy and 1 prior line of taxane-based chemotherapy for mCRPC. Interim efficacy results from the TRITON2 study in breast cancer gene (BRCA)-mutated mCRPC patients administered rucaparib 600 mg twice a day (BID) demonstrated a 44% (95% confidence interval [CI]: 31 to 57) overall response rate (ORR) by independent radiology review (IRR) in 62 patients evaluable by Response Evaluation Criteria in Solid Tumors (RECIST Version [v] 1.1) modified according to Prostate Cancer Working Group Guidelines Version 3 (PCWG3), combined with evaluation of bone disease according to PCWG3 (mRECIST/PCWG3); ORR by IRR was similar in patients with germline versus somatic BRCA mutation.[6] Activity was also observed in patients with other DDR gene alterations. In addition, the PARP inhibitors olaparib and niraparib have shown evidence of clinical activity in mCRPC patients with DDR alterations.[7, 8] These findings provide

[1] Gene and protein names should typically 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.

compelling evidence for use of a PARPi in a selected population of mCRPC patients with predicted loss-of-function alterations in DDR genes, including BRCA1/2.

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 AR pathway, abiraterone acetate and enzalutamide.[9-13] Based on their tolerability and proven efficacy in the prechemotherapy 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 to 18 months on treatment.

Recent studies have demonstrated complex cross-talk between ARs and the DDR pathway. The bulk of evidence suggests regulation of double strand break (DSB) repair by the AR;[14-17] therefore, AR antagonists used in prostate cancer treatment cause irreparable DSBs and point to a viable synergy between AR-directed therapy and PARP inhibitors, independent of homologous recombination gene mutations.[14] This hypothesis has been clinically tested in a randomized study where the combination of olaparib and abiraterone in unselected mCRPC patients was found to be superior to the abiraterone alone arm with a hazard ratio (HR) of 0.65 (median radiographic progression-free survival [rPFS] 13.8 vs. 8.2 months).[18]

Novel therapies that provide robust clinical benefit and have a manageable safety profile are still needed for patients with advanced mCRPC. Therefore, evaluation of rucaparib in combination other anticancer therapies, such as an AR antagonist or other therapeutic option, represents a viable treatment option, including for patients with and without evidence of HRD.

### 1.1.1 Rucaparib

Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, that play a critical role in base excision repair (BER).[23]

Rucaparib (Rubraca®) is approved in the US for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with 2 or more prior chemotherapies; for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with AR-directed therapy and a taxane-based chemotherapy; and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response (PR) to platinum-based chemotherapy.[6] Rucaparib is also approved in the European Union (EU) 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, and for maintenance treatment of adult patients with platinum-sensitive recurrent EOC, FTC, or PPC who are in response

(complete or partial) to platinum-based chemotherapy.[24] In addition, rucaparib is being developed for the treatment of cancer associated with HRD, defined by the presence of a deleterious mutation in BRCA1, BRCA2, or other HRR genes, and/or high percentage of tumor genome with loss of heterozygosity (LOH), which is a phenotypic consequence of HRD.

A brief overview of data from nonclinical and clinical studies are provided below and described in detail in the rucaparib Investigator's Brochure (IB).

#### 1.1.1.1 Nonclinical Experience

The results from nonclinical studies are consistent with the 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 models, 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.

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-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) 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. Rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate-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) 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 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 embryotoxic. 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.[25-28]

#### 1.1.1.2 Clinical Experience

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer with and without evidence of HRD. Rucaparib clinical studies have evaluated (and continue to evaluate) patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer in both the treatment and maintenance settings.

Rucaparib is being evaluated as treatment for patients with mCRPC, both as monotherapy and in combination with nivolumab.

Clinical pharmacology studies in patients with advanced solid tumors have evaluated rucaparib drug-drug interactions (DDIs) and mass balance and drug metabolism. Additional clinical pharmacology studies continue to characterize rucaparib DDIs, as well as rucaparib PK in special populations.

Additional studies of rucaparib as monotherapy and in combination with other anticancer therapies are planned in ovarian, prostate, and bladder cancers, as well as other tumors.

Information regarding clinical studies with rucaparib is available in the IB.

##### 1.1.1.2.1 Overview of Pharmacokinetics and Drug-drug Interactions

Assessment of rucaparib PK in cancer patients showed an approximate dose proportional exposure after once a day (QD) or BID dosing, rapid absorption with maximum concentration ($C_{max}$) achieved within 1.5 to 6 hours. The oral bioavailability was 36% and half-life ($t_{1/2}$) was approximately 24 hours. Rucaparib was moderately bound to human plasma proteins in vitro (70%).

At a dose of 600 mg BID rucaparib, steady state was achieved after approximately 1 week with approximately 4-fold accumulation. A high-fat meal increased the $C_{max}$ and area under the concentration-time curve from 0 to 24 hours ($AUC_{0-24}$) of rucaparib by 20% and 38%, respectively, as compared with that under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

In vitro, rucaparib showed slow enzymatic turnover in human liver microsomes and hepatocytes. Recombinant CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. In cancer patients, M324, a carboxylic acid, was a major inactive metabolite of rucaparib.

Drug interactions with rucaparib as a substrate were assessed in a population PK (PPK) analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultrarapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyper-inducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. 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. Although in vitro rucaparib

metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. No rucaparib dose adjustment is recommended when concomitantly administered with CYP inhibitors or inducers.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI.

Results from Study CO-338-044 evaluating potential DDI with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on the PK of oral digoxin (a P-gp substrate). Caution should be exercised in the concomitant use of drugs that are sensitive clinical substrates of the above CYP enzymes (Section 6.4).

In another DDI study (Study CO-338-095) in cancer patients, effects of rucaparib on oral rosuvastatin as BCRP substrate and oral contraceptives were determined following 14 days of dosing at 600 mg BID. Rucaparib weakly inhibited BCRP and caused mild increases in plasma exposures to ethinylestradiol and levonorgestrel.

In Study CO-338-078, PK of a single dose of rucaparib was compared between cancer patients with normal hepatic function and moderate hepatic impairment. Patients with moderate hepatic impairment showed approximately 46% increase in area under the concentration-time curve from 0 to infinity ($AUC_{0\text{-}inf}$) without apparent change in $C_{max}$.

Details of these clinical DDI studies are provided in the rucaparib IB.

#### 1.1.1.2.2 Overview of Efficacy

Rucaparib was originally approved by the US Food and Drug Administration (FDA) in December 2016 as monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. As of May 2018, rucaparib was approved by the European Commission for the same indication with the exception that patients must be intolerant to subsequent platinum-based chemotherapy.[29] The recommended dose of rucaparib is 600 mg BID.

The primary outcome measure on which approval by FDA for the treatment indication was based is investigator-assessed ORR per RECIST v1.1, with ORR by central independent radiological review conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR by independent review was 41.5%, confirming the results of investigator assessment for this endpoint.[30] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

In April 2018, rucaparib was approved by the US FDA for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[31] This approval was based on Study CO-338-014 (ARIEL3), a randomized, placebo-controlled Phase 3 study.

In May 2020, rucaparib was approved by the US FDA for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with AR-directed therapy and a taxane-based chemotherapy. The approval was based on Study CO-338-052 (TRITON2), for which the primary outcome measure was ORR by IRR evaluable by mRECIST/PCWG3; ORR by IRR was 44% at the recommended dose of rucaparib 600 mg BID.[6]

#### 1.1.1.2.3 Overview of Safety

Results of a recent integrated safety analysis in over 1,000 patients with ovarian or prostate cancer who received 600 mg BID rucaparib in the treatment or maintenance setting showed that the most common treatment-emergent adverse events (TEAEs) reported were primarily mild to moderate (Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased, decreased appetite, and dysgeusia. The most common TEAE ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue. Section 6.6 of the rucaparib IB serves as guidance to the investigator on adverse drug reactions (ADRs) for rucaparib, based on incidence of TEAEs by all National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grades and by ≥ Grade 3.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI),[32, 33] and few patients discontinued rucaparib due to ALT/AST elevations.[34, 35] Similarly, elevations in creatinine were self-limiting and generally stabilized over time. The majority of creatinine elevations were Grade 1 or Grade 2. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib were not accompanied by changes in blood urea nitrogen (BUN) and did not lead to discontinuation of rucaparib treatment. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters (Section 1.1.1.1).

An updated analysis of safety presented in the US prescribing information[6] and the EU Summary of Product Characteristics (SmPC)[24] demonstrate that safety results in ovarian cancer patients treated with rucaparib have remained consistent with those previously reported, and that the safety profile is consistent across both the treatment and maintenance indications for rucaparib in ovarian cancer and in the treatment of mCRPC.

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

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 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 8.7. Also, refer to the rucaparib IB for information regarding the AESI of pneumonitis.

### 1.1.2 Enzalutamide

Enzalutamide is a next-generation anti-androgen that acts on multiple steps of AR signaling within prostate cancer tumor cells.[20] It is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), that develops after patients are treated with luteinizing hormone-releasing hormone (LHRH) therapy. Further details about enzalutamide, including clinical efficacy, are available in the prescribing information.[19]

#### 1.1.2.1 Overview of Pharmacokinetics

Following oral administration of enzalutamide in patients with mCRPC, the time to maximum concentration ($t_{max}$) was 1 hour. The steady-state of enzalutamide was reached after 28 days dosing with 8.3-fold accumulation. Enzalutamide showed approximately dose proportional steady-state PK over the daily dose range of 30 to 360 mg.

Enzalutamide is primarily eliminated by hepatic metabolism. N-desmethyl enzalutamide is a major active metabolite. The $C_{max}$ values of enzalutamide and N-desmethyl enzalutamide were 16.6 µg/mL and 12.7 µg/mL, respectively. The terminal half-lives were approximately 5.8 days for enzalutamide and 7.8 to 8.6 days for N-desmethyl enzalutamide. A high-fat meal did not alter the area under the concentration-time curve (AUC) of enzalutamide or N-desmethyl enzalutamide. Enzalutamide can be dosed with or without food.

Based on clinical DDI studies, co-administration of strong CYP2C8 inhibitor gemfibrozil increased the AUC of enzalutamide plus its active metabolite N-desmethyl enzalutamide by

2.2-fold. Co-administration of rifampin, a strong CYP3A4 inducer and a moderate CYP2C8 inducer, decreased the AUC of enzalutamide and N-desmethyl enzalutamide by 37%. Strong CYP2C8 inhibitors and strong CYP3A4 inducers should be avoided. Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 should be avoided.

Effect of organ dysfunction on PK was evaluated in a population PK analysis. The apparent clearance (CL/F) of enzalutamide was similar in subjects with pre-existing mild and moderate renal impairment (creatinine clearance [CrCL] 30 to < 90 mL/min) compared to subjects with normal renal function (CrCL ≥ 90 mL/min). The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in subjects with mild, moderate, or severe baseline hepatic impairment compared to subjects with normal hepatic function.

No clinically significant PK covariates have been identified.

The effect of enzalutamide 160 mg QD on the QT interval corrected for heart rate (QTc) was evaluated in patients with mCRPC. No large QTc prolongation was observed (ie, greater than 20 ms), but small increases (ie, < 10 ms) due to enzalutamide cannot be excluded.

#### 1.1.2.2 Overview of Efficacy

The efficacy and safety of enzalutamide in 4,692 patients with CRPC were demonstrated in 4 randomized, multicenter clinical studies: AFFIRM, PREVAIL, TERRAIN and PROSPER. All patients continued on gonadotropin releasing hormone (GnRH) therapy or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate glucocorticoids. Further details are available in the prescribing information.[19]

#### 1.1.2.3 Overview of Safety

Seizure occurred in 0.4% of patients receiving enzalutamide. In patients with predisposing factors, seizures were reported in 2.2% of patients. There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed in the clinical studies with pharyngeal edema seen in postmarketing cases. Patients receiving enzalutamide also had a higher rate of ischemic heart disease as well as falls and fractures. The most common adverse reactions are asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache, and weight decrease. Further details including management of these adverse effects are available in the prescribing information.[19]

### 1.1.3 Abiraterone

Abiraterone is an inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), an enzyme expressed in testicular, adrenal, and prostatic tumor tissues, which is required for androgen biosynthesis. The blockade of nongonadal androgen production is a key factor in treating

CRPC, since prostate cancer cells are dependent on androgens. Abiraterone is indicated in combination with prednisone for the treatment of patients with mCRPC and metastatic high-risk castration-sensitive prostate cancer (CSPC).[21] The addition of prednisone is to prevent mineralocorticoid excess-related AEs (such as hypertension, hypokalemia and fluid retention), resulting from CYP17 inhibition.[22] Further details about abiraterone, including clinical efficacy, are available in the prescribing information.[21]

#### 1.1.3.1 Overview of Pharmacokinetics

Following oral administration of abiraterone acetate at 1,000 mg QD to patients with mCRPC, the steady-state $C_{max}$ was 226 ng/mL and the AUC was 993 ng hr/mL with a 2-fold accumulation. Further increase of dose to 2,000 mg resulted in minimal increase (8%) in AUC.

Significant food effect on PK was observed. In healthy subjects, a low-fat meal (7% fat, 300 calories) increased abiraterone $C_{max}$ and AUC by 7- and 5-fold, respectively; while a high-fat meal (25% fat, 491 calories) increased $C_{max}$ and AUC by 17- and 5-fold, respectively. When abiraterone acetate was dosed 2 hours after or 1 hour before a medium fat meal, abiraterone AUC increased by approximately 7- or 1.6-fold, respectively. In patients with mCRPC, systemic exposures of abiraterone at steady state were similar when abiraterone acetate was taken with low-fat meals and increased by approximately 2-fold when taken with high-fat meals compared to when taken at least 2 hours after a meal and at least 1 hour before a meal. As a result, abiraterone acetate must be taken on an empty stomach with water at least 1 hour before or 2 hours after a meal.

Abiraterone has high plasma protein binding (> 99%) and large apparent steady-state volume of distribution. At clinical exposures, abiraterone acetate and abiraterone are not P-gp substrates; abiraterone acetate is a P-gp inhibitor.

After oral administration, abiraterone acetate is hydrolyzed to the active metabolite abiraterone, which is further metabolized to 2 inactive metabolites abiraterone sulphate and N-oxide abiraterone sulphate. The formation of abiraterone is likely mediated by esterases, and CYP3A4 and SULT2A1 are responsible for the subsequent N-oxidation and formation of sulphate metabolites.

In patients with mCRPC, the $t_{1/2}$ of abiraterone in plasma is approximately 12 hours. Following an oral dose of $^{14}$C-abraterone acetate, approximately 88% of the radioactive dose was recovered in feces and approximately 5% in urine.

Subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment showed 1.1, 3.6, and 7-fold increases in systemic exposure to abiraterone, respectively, compared to subjects with normal hepatic function following a single oral dose of 1,000 mg abiraterone acetate. Patients with end-stage renal disease on hemodialysis showed no apparent PK difference than patients with normal renal function.

In vitro studies showed that abiraterone has the potential to inhibit CYP1A2, CYP2D6 CYP2C8, and to a lesser extent CYP2C9 CYP2C19, and CYP3A4/5. Clinically, the $C_{max}$ and AUC of dextromethorphan, a CYP2D6 substrate, increased by 2.8- and 2.9-fold,

respectively, when co-administered with 1,000 mg abiraterone acetate daily. However, no clinical inhibition of CYP1A2 was observed when theophylline was used as a CYP1A2 DDI probe. Abiraterone is a CYP3A4 substrate. While co-administration of ketoconazole (a strong CYP3A4 inhibitor) showed no effect on abiraterone PK, a 55% decrease in mean abiraterone AUC was observed when abiraterone acetate was co-administered with rifampin (a strong CYP3A4 inducer). Abiraterone was a weak CYP2C8 inhibitor and increased the AUC of pioglitazone by 46%.

The QT prolongation potential was assessed following abiraterone 1,000 mg QD in patients with mCRPC. No large change in the QTc interval from baseline (ie, > 20 ms), however, small increases in the QTc interval (ie, < 10 ms) due to abiraterone acetate cannot be excluded.

#### 1.1.3.2 Overview of Efficacy

Abiraterone was tested in a Phase 3 randomized, placebo-controlled study with a total of 1,195 mCRPC patients to demonstrate its superiority over placebo with a 57% reduction in the risk of radiographic progression or death (HR 0.43; 95% CI: 0.35 to 0.52; $p < 0.001$) and an estimated 25% decrease in the risk of death (HR 0.75; 95% CI: 0.61 to 0.93; $p = 0.009$).[12, 36] Additional details are provided in the prescribing information.[21, 37]

#### 1.1.3.3 Overview of Safety

Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition, and therefore should be used with caution in patients with a history of cardiovascular disease. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Adrenocortical insufficiency has been reported in clinical studies in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred in clinical studies with abiraterone. Aside from these, the most common side effects were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. Additional details are provided in the prescribing information.[21]

## 1.2 Study Rationale

The study will initially evaluate the combinations of rucaparib with 2 widely used AR-directed therapies, enzalutamide and abiraterone. Subsequent arms of the study may include other combination partners (eg, AR inhibitors in development or immune modulators such as checkpoint inhibitors). The primary goal of this study is to investigate potential DDI and safety/tolerability in the 2 combinations, and also preliminary efficacy. The outcome of these studies will be used to support larger studies to investigate these combinations in mCRPC.

### 1.2.1 Known and Potential Risks and Benefits to Patients

While there is scientific rationale and clinical precedence of benefit for the combination of PARPi and AR-directed therapy, as elucidated above, the combination of rucaparib with either enzalutamide or abiraterone has not been previously tested and thus clinical benefit of these combinations has not been established. In this trial, both enzalutamide and abiraterone will be administered at their approved monotherapy doses. The starting dose of rucaparib (further detailed in Section 1.2.3) in each arm has been chosen based on review of the individual agent safety profiles, with an aim towards minimizing overlapping toxicities. Escalation of rucaparib dose will take into account safety and tolerability observed at prior dose levels.

### 1.2.2 Rationale for the Study Design

The primary objectives for this study are to evaluate the PK, safety and tolerability of rucaparib in combination with other anticancer therapies for the treatment of mCRPC.

The study is therefore divided into an initial PK assessment phase, which also evaluates safety/tolerability in addition to PK, and a dose expansion phase to further characterize PK and safety/tolerability if needed. The PK assessment will incorporate a run-in phase of rucaparib alone in the first week, in order to assess the impact on rucaparib PK once the combination partner is also introduced.

In Arm A, based on the individual safety profiles of both rucaparib and enzalutamide, no significant overlap in toxicity is expected. Therefore, the approved monotherapy dose of each agent will be the starting dose for the initial combination evaluation. Patients will be closely monitored for safety and tolerability and the dose of rucaparib may be reduced, if appropriate, based on emerging safety data. Preliminary assessment of the metabolic profile of rucaparib and enzalutamide indicates that rucaparib exposure may be diminished due to CYP3A4 induction by enzalutamide (detailed in Section 1.2.3). Therefore, depending on the PK profile of rucaparib, and taking into account the emerging safety/tolerability data, rucaparib dose may be escalated beyond the starting dose of 600 mg BID. Rucaparib escalation, up to a maximum dose of 1,000 mg BID rucaparib, may be explored based on emerging PK, safety and tolerability data. The potential increase in rucaparib dose will be proportional to the decrease in exposure (relative to expected exposure for monotherapy) seen at the previous dose level.

In Arm B, the target combination doses will be the approved monotherapy doses for abiraterone and rucaparib. However, as there is potential for overlapping toxicities with this combination (detailed in Section 1.2.3), the initial starting dose for rucaparib will be 400 mg BID, with escalation planned to 600 mg BID if the initial dose level is deemed safe and tolerable. If a dose of 600 mg BID rucaparib in combination with the standard dose of abiraterone is not tolerated, a dose of 500 mg BID rucaparib in combination with the standard dose of abiraterone may be explored. In the event that there is unexpected lower exposure of rucaparib with co-administration of abiraterone, the dose of rucaparib may be increased beyond 600 mg BID, similar to the approach outlined for Arm A.

Dose escalation or de-escalation strategy for both Arms A and B is further detailed in Section 3.3.

Once a safe and tolerable dose combination is established, for both Arm A and Arm B, PK and safety/tolerability characterization may be conducted with up to 12 additional patients in the dose expansion phase, particularly if PK in the initial PK assessment phase is variable or additional safety information is required.

### 1.2.3 Dose Rationale

Dose determination in each arm of the study will be performed as described in Section 3.3. All patients in Arm A will receive enzalutamide at 160 mg QD and all patients in Arm B will receive abiraterone at 1,000 mg QD with 5 mg prednisone BID. Starting dose of rucaparib is 600 mg BID in Arm A and 400 mg BID in Arm B.

**Arm A:**

In vitro, rucaparib is metabolized by CYP2D6, and to a lesser extent by CYP1A2 and CYP3A4. Enzalutamide is a strong clinical inducer of CYP3A4,[38] thus enzalutamide may result in reduced rucaparib exposure when administered in combination.

Based on clinical safety data, significant overlapping toxicities between enzalutamide and rucaparib are not expected. Based on the available data, a combination of approved dose levels of enzalutamide 160 mg QD and rucaparib 600 mg BID administered with or without food is anticipated to be a safe starting dose.

Another justification for starting the first dose cohort at the full doses of rucaparib and enzalutamide is the long $t_{1/2}$ of enzalutamide (5.8 days) and its active metabolite N-desmethyl enzalutamide (7.8 to 8.6 days). The plasma exposure of enzalutamide and N-desmethyl enzalutamide increase slowly following enzalutamide treatment, and it takes approximately 40 days to reach the steady state. Therefore, any exacerbation of overlapping toxicities is likely to be gradual.

Enzalutamide starting dose will be fixed at the approved dose of 160 mg QD. No dose adjustment is planned for the starting dose of enzalutamide.

**Arm B:**

Abiraterone administration is not expected to have any impact on rucaparib exposure. However, anemia, hypercholesterolemia, increased alkaline phosphatase (ALP), nausea, vomiting, fatigue, diarrhea and upper respiratory tract infections have been reported in patients receiving abiraterone, as well as for patients receiving rucaparib. A conservative starting dose of rucaparib 400 mg BID (~ 67% of approved starting dose) and the approved starting dose of abiraterone 1,000 mg QD are selected for initiation of Arm B in the dose escalation phase.

Abiraterone acetate starting dose will be fixed at the approved dose of 1,000 mg QD. No adjustment is planned for the starting dose of abiraterone acetate.

### 1.2.4 Rationale for Duration of Treatment

Patients will be on study as long as they benefit from the study treatment or unless they withdraw from study.

A 1-week run-in period with rucaparib alone prior to the start of combination therapy allows for the assessment of rucaparib PK in the absence of either enzalutamide or abiraterone in Arms A and B respectively.

In Arm A, the dose-limiting toxicity (DLT) window is 8 weeks (Cycles 1 and 2). This is justified as enzalutamide and its major active metabolite N-desmethyl enzalutamide have long half-lives. Evaluation and assessment over an 8-week period will allow for adequate PK and DLT assessments.

In Arm B, due to the shorter $t_{1/2}$ of abiraterone, a 4-week period is expected to suffice for assessment of PK and DLTs.

# 2 STUDY OBJECTIVES

Primary, secondary, and exploratory objectives and endpoints are shown in Table 2-1.

### Table 2-1. Study Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Primary Endpoint** |
| • To evaluate the PK, safety and tolerability of rucaparib in combination with other anticancer agents for mCRPC. | • Minimum concentration ($C_{min}$) of rucaparib and its metabolite M324<br>• Safe and tolerable dose of rucaparib in combination with other anticancer agents for mCRPC |
| **Secondary Objectives** | **Secondary Endpoints** |
| • To evaluate the preliminary efficacy of rucaparib with each of its combination partners. | • Best overall response as assessed by investigator summarized by ORR (as measured by modified RECIST v1.1 (mRECIST)/PCWG3 criteria; Appendix 1) at the optimal combination dose in each arm<br>• Change from baseline PSA levels |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| • To evaluate the PK of anticancer drugs in combination with rucaparib. | • $C_{min}$ of combination drugs (and metabolites if applicable) |
| • To assess the relationship between genomic alterations detected in tissue or blood with clinical outcomes to treatment | • Association between genomic alterations and ORR and PSA responses |
| • To assess the relationship between changes in circulating tumor DNA (ctDNA) profiles over time and clinical outcomes to treatment | • Changes in genomic alterations as assessed by ctDNA over time |

# 3 STUDY DESIGN

This is a Phase 1b, open-label, platform study with multiple treatment arms evaluating the PK, DDIs, safety, tolerability and preliminary efficacy of rucaparib in combination with a second anticancer therapy in patients with mCRPC. Each arm consists of a preliminary phase designed to assess PK and safety and tolerability of rucaparib in combination with other anticancer agents, followed by an expansion phase (if needed) to further evaluate PK, safety, tolerability and preliminary efficacy of the combination.

## 3.1 Screening Period

All mCRPC patients will undergo screening assessments between Day -28 and Day -1 after they sign an Informed Consent Form (ICF) and prior to any study-specific procedures being performed.

Refer to the inclusion/exclusion criteria (Section 4.2 and Section 4.3) for details.

## 3.2 Enrollment

Eligible patients will be enrolled into the PK assessment phase or the dose expansion phase (after a combination dose is established) across the treatment arms. If a patient appears to be eligible for more than one treatment arm that is open to enrollment, the investigator will be responsible for selecting the treatment arm for the patient. However, enrollment into Arm A will be prioritized over Arm B until the objectives for Arm A have been achieved. No patient randomization is planned.

## 3.3 Treatment Period

As of the implementation of Protocol Amendment 2, during and at the end of treatment, a more limited number of assessments will be performed compared to previously; however, an appropriate level of safety monitoring will remain in place. A revised Schedule of Assessments (SOA) is provided in Section 7.1; this replaces all prior SOAs and should be followed for all patients who remain on treatment.

During the treatment phase (continuous 28-day treatment cycles), patients will be monitored for safety and efficacy. Assessments during the treatment phase will include AEs, complete blood count (monthly assessment advised), and study drug administration/accountability; in addition, disease assessments (imaging/PSA), clinical chemistry, urinalysis, and vital signs will be performed per local standard of care practices. Disease/tumor assessments per mRECIST/PCWG3 criteria will be performed according to local standard of care per investigator.

Patients starting on the study in either the PK assessment phase or the dose expansion phase will be administered rucaparib alone for 1 week. After completing this run-in period, they will immediately begin continuous 28-day treatment cycles of rucaparib and the combination drug.

**PK Assessment Phase:**

Doses of rucaparib may be modified in this phase from the starting dose; however, the dose of its combination partner (either enzalutamide in Arm A or abiraterone co-administered with prednisone in Arm B) will remain fixed.

Arm A: Six patients will be enrolled at the standard monotherapy dose of enzalutamide and starting dose of rucaparib of 600 mg BID. If no significant PK interaction is observed and safety and tolerability is within acceptable guidelines (Section 5.6), no further dose titration will be done. However, if PK interactions indicate the concentration of rucaparib is 25% to 50% of the expected rucaparib exposure in monotherapy, then a higher dose of rucaparib will be considered, to a maximum dose of 1,000 mg BID, also taking safety and tolerability into account. The increase in dose will be scaled to be proportional to the decrease in expected exposure. In the event ≥ 1 of 6 patients experiences a DLT (as defined in Section 5.6), a lower dose of rucaparib may be explored, with subsequent dose cohorts enrolling a minimum of 3 patients and a maximum of 6 patients, unless the rucaparib dose is at the minimal dose of 300 mg BID.

Arm B: Three patients will be enrolled at the starting dose of 400 mg BID rucaparib in combination with the standard monotherapy dose of abiraterone. If there is no DLT (as defined in Section 5.6) observed in any of these 3 patients, the next higher dose of 600 mg BID rucaparib will be explored. If one patient develops a DLT, the cohort will be expanded to 6 patients. If DLTs are observed in ≥ 1 of 3 to 6 patients in a given dose cohort, no further dose escalation will be performed. If a dose of 600 mg BID rucaparib in combination with the standard dose of abiraterone is not tolerated, a dose of 500 mg BID rucaparib in combination with the standard dose of abiraterone may be explored. The dose of rucaparib may also be increased beyond 600 mg BID if there is unexpected lower exposure with co-administration of abiraterone, similar to the approach outlined for Arm A. Each dose cohort in this arm will enroll a minimum of 3 patients and a maximum of 6 patients.

Prior to initiating treatment at each new combined dose level or prior to expanding an existing dose level, a teleconference with the Dose Cohort Review Committee (Section 3.6) will be held to review patient data.

The combination dose for evaluation in the expansion phase will be selected based on overall safety and tolerability, PK, as well as any efficacy observed.

Disease/tumor assessments and PSA measurements will be performed according to local standard of care per investigator. Any drug modifications (interruption, dose reduction, or discontinuation) should be documented in the electronic Case Report Form (eCRF, see Section 10.5) and source documents.

Patients will receive rucaparib and the combination drug until confirmed radiologic disease progression assessed by investigator based on mRECIST/PCWG3 (Appendix 1), 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.

Sparse PK samples will be collected from all patients for assessments of PK and DDIs (Table 7-2).

**Expansion Phase:**

Once the optimal combination dose has been provisionally determined, up to 12 additional patients may be enrolled and treated at that dose combination to further characterize PK, safety and tolerability, in order to establish that this is the optimal dose combination for future clinical studies.

**Pharmacokinetics and Drug-Drug Interaction Assessment**:

In both the initial PK assessment phase as well as the expansion phase, PK assessment will start with a 1-week run-in period, during which patients will receive rucaparib treatment only. Predose rucaparib PK samples at selected timepoints will be collected. This will be followed by continuous treatment of rucaparib and the combination drug in 28-day treatment cycles, with predose PK samples collected for rucaparib and the combination drug at selected timepoints.

## 3.4 End of Treatment and Follow-up

As of the implementation of Protocol Amendment 2, more limited post-treatment assessments will be performed while maintaining appropriate safety monitoring. A revised SOA is provided in Section 7.1; this replaces prior SOAs.

Patients experiencing disease progression by mRECIST/PCWG3, as assessed by the investigator, will be discontinued from study treatment and enter into follow-up with the exception defined in Section 3.5.

Upon treatment discontinuation, patients will have an End-of-Treatment (EOT) Visit and a 28-day Follow-up Visit. Ongoing serious adverse events (SAEs), AESIs, and treatment-related Grade 3/4 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 assessed as potentially related to study drug should be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database.

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 similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28 days after the last dose of study drug). After the 28-day Follow-up Visit, only **serious** pneumonitis or similar events assessed as **potentially related to study drug** should be reported per Clovis Oncology PV requirements.

## 3.5 Treatment Beyond Disease Progression

If the patient has met criteria for radiologic progression by mRECIST/PCWG3, but the patient is still receiving benefit from the study drugs according to the investigator (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), then continuation of treatment will be considered upon discussion with the medical monitor (see Section 5.11). The patient must consent prior to continuing treatment with the study drugs.

## 3.6 Dose Cohort Review Committee

This committee will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites. It will be responsible for reviewing safety, PK, and preliminary efficacy data at regular intervals throughout the study. Prior to initiating treatment at a new dose level or expanding a dose level, a safety teleconference will be held to review patient data, including, but not limited to, demographics, PK results, study drug dosing, concomitant medications, hematology and serum chemistry, and AEs. The discussion and agreement to escalate or reduce the rucaparib dose and/or expand an existing dose level will be documented.

## 3.7 Removal of Patients From Therapy or Assessment

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, where acceptable according to national law and/or local regulations, at the request of their legally authorized representative;
- Progression of patient's underlying cancer per mRECIST and/or PCWG3 criteria as assessed by the investigator, unless the patient continues to derive clinical benefit from the study drug(s) according to the investigator, the investigator has consulted with the sponsor's medical officer or designee, and the patient has provided additional consent for treatment beyond progression at the next study visit;
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient. If it is determined that one of the study drugs in the combination is posing a safety risk and that study drug is permanently discontinued, administration of the other study drug may continue if none of the other withdrawal

criteria have been met and the investigator believes that the patient may continue to receive benefit;

- Any concomitant 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; or
- The study is terminated.

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. The sponsor will store samples for up to 7 years after the study is over and any remaining samples will be destroyed at that time. Information that is collected while the patient has consented to be in the study cannot be withdrawn. Details are provided in the ICF.

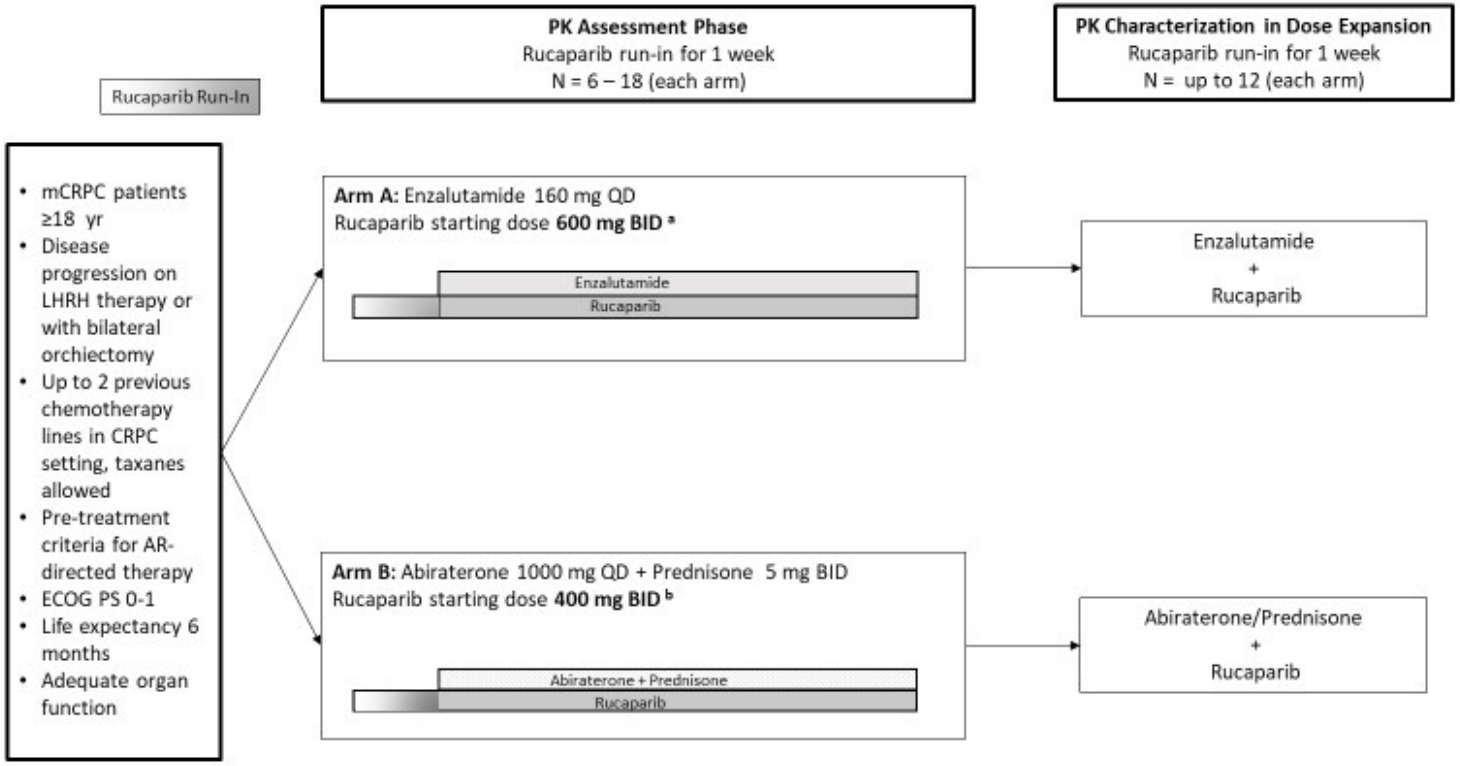
If the patient withdraws consent to continue in the study or discontinues the study for another reason it will be documented on the appropriate eCRF (see Section 10.5). A patient may withdraw consent to participate in an additional or optional part of a study that has a corresponding consent (ie, optional tumor biopsy) yet continue to participate and be treated/followed in the main part of the study.

The sponsor may discontinue the study early for any of the reasons noted in Section 10.6.

## 3.8 Study Schema

The study schema in Figure 3-1 summarizes the treatment design of the study.

## Figure 3-1. Study Schema




**NOTE: For patients remaining on treatment as of the implementation of Protocol Amendment 2, during and at the end of treatment, a more limited number of assessments will be performed compared to previously; however, an appropriate level of safety monitoring will remain in place. A revised SOA is provided in Section 7.1; this replaces all prior SOAs and should be followed for all patients who remain on treatment.**

Abbreviations: AR = androgen receptor; BID = twice a day; CRPC = castration-resistant prostate cancer; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group performance status; LHRH = luteinizing hormone–releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; PK = pharmacokinetic; QD = once a day; SOA = Schedule of Assessments.

[a] Rucaparib dose may be reduced to < 600 mg BID if more than one patient experiences a DLT. If rucaparib exposure is lower than expected with co-administration of enzalutamide, rucaparib dose may be increased proportional to the decrease in exposure, to a maximum of 1,000 mg BID.

[b] Rucaparib dose will be escalated from 400 mg BID to 600 mg BID, with a possible de-escalation to 500 mg BID. The dose of rucaparib may also be increased if there is unexpected lower exposure with co-administration of abiraterone, similar to the approach described for Arm A.

## 3.9 End of Study

The study will close when all enrolled patients have discontinued treatment and completed the 28-day Safety Follow-up Visit, or have withdrawn consent for the study (Section 3.7), or the sponsor terminates the study for any reason as noted in Section 10.6.

# 4 STUDY POPULATION

## 4.1 Number of Patients and Sites

For each combination arm, the PK assessment cohort will include 6 to 18 patients (1 to 3 dose cohorts), and the expansion phase will include up to 12 patients. The number of patients in each cohort may increase if some patients are not DLT-evaluable, thereby requiring additional patients to be enrolled into the study. The total enrollment planned for Arm A and Arm B will be up to 60 patients. There will be approximately 10 investigative sites in the US.

## 4.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria. Unless otherwise specified, the criteria below apply to patients enrolling into all parts of the study.

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF prior to any study-specific evaluation.
2. Be ≥ 18 yrs 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).
4. Surgically or medically castrated, with serum testosterone levels of ≤ 50 ng/dL (1.73 nM). For patients currently being treated with LHRH agonists (ie, patients who have not undergone an orchiectomy), therapy must be continued throughout the study.
5. Be either AR-directed therapy naïve or have received 1-2 lines of AR-directed therapy in the castration-resistant setting. If most recently treated with enzalutamide in the castrate-resistant setting, they must have been had no enzalutamide treatment for at least 6 weeks prior to the first planned dose of rucaparib. If most recently treated with an AR-directed therapy other than enzalutamide, patients must have ceased AR-directed therapy treatment for at least 4 weeks prior to the first planned dose of rucaparib.
6. Have disease progression after initiation of most recent therapy 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 mRECIST
   c. Radionuclide bone scan: at least 2 new metastatic lesions

7. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to enrollment:
   a. Bone Marrow Function
      i. ANC ≥ $1.5 \times 10^9$/L;
      ii. Platelets ≥ $100 \times 10^9$/L;
      iii. Hemoglobin ≥ 10 g/dL independent of transfusion ≤ 14 days prior to screening hemoglobin assessment. Transfusions are not permitted between the screening hemoglobin assessment and the first dose of rucaparib.
   b. Hepatic Function
      i. AST and ALT ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN;
      ii. Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome;
      iii. Serum albumin ≥ 30 g/L (3.0 g/dL).
   c. Renal function
      i. Serum creatinine ≤ 1.5 × ULN; OR
      ii. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft-Gault formula
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 within 14 days prior to the first dose of rucaparib (Appendix 2).
9. Have a life expectancy of at least 6 months.
10. Patients with human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) infection may be enrolled if they have undetectable viral load with antiviral medication and if the antiviral medications do not interfere with any of the study drugs.

## 4.3 Exclusion Criteria

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

1. Active second malignancy, ie, patient known to have potentially fatal cancer present for which he may be (but not necessarily) currently receiving treatment. Exceptions are patients with history of malignancy that has been successfully treated, with no evidence of active cancer for 3 years prior to enrollment, or surgically cured and/or low risk tumors, such as non-melanoma skin cancers.
2. Have received greater than 2 previous lines of chemotherapy for mCRPC, including taxanes.
3. Prior treatment with any PARP inhibitor.
4. Spinal cord compression, symptomatic and/or untreated central nervous system (CNS) metastases or leptomeningeal disease. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
5. Severe concurrent disease, infection, comorbidities.

6. Known hepatic disorder that would affect drug metabolism or gastrointestinal disorders that would potentially alter absorption.
7. Any clinically significant cardiovascular disease.
8. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with ingestion or absorption of rucaparib.
9. Received anticancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs (other than GnRH therapy or approved bone-targeting agents) ≤ 14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment > NCI CTCAE v5.0 Grade 1, with the exception for alopecia and Grade 2 peripheral neuropathy.
10. Nonstudy related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must be sufficiently recovered and stable before treatment administration.
11. Taking any concomitant medications or herbs that could confound PK assessment.
12. 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 ineligible for entry into the study.
13. Refusal to undertake the following measures for the duration of the study and after the last dose of study drug for the time period specified:
    a. Using a condom during sex while being treated and for 3 months after the last dose of study drug,
    b. Abstaining from semen donations during treatment and for 3 months after the last dose of rucaparib,
14. Those with female partners of childbearing potential may be enrolled if they are:
    a. Documented to be surgically sterile (ie, vasectomy); or
    b. Committed to practicing true abstinence during treatment and for 3 months after the last dose of study drug; or
    c. Committed to using a highly effective method of contraception (Section 4.4) with their partner during treatment and for 3 months following the last dose of study drug.
15. Cohort-specific exclusion criteria:
    a. Arm A: Patients with
        i. A history of seizures or traumatic brain or head injury, and/or receiving concomitant medication that lowers seizure thresholds; or
        ii. Uncontrolled or suboptimally controlled ischemic heart disease, history of myocardial infarction/unstable angina, coronary vascular intervention such as percutaneous coronary intervention (PCI), stent placement or coronary artery bypass graft (CABG) within past 1 year, stable angina or New York Heart Association (NYHA) Class 2 to 4 heart failure.
    b. Arm B: Patients with:
        i. Mean resting QTc > 470 msec obtained from 3 consecutive ECGs;

ii. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third degree heart block, etc.;
iii. Any history of syncope of suspected/confirmed cardiovascular etiology, ventricular arrhythmia of pathologic origin, uncontrolled atrial fibrillation, or sudden cardiac arrest within the past 1 year;
iv. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age, or any concomitant medication known to prolong the QT interval;
v. History of hypokalemia < 3 mmol/L, uncontrolled hypertension (defined as median BP ≥ 160/90 mm Hg on three serial measurements performed at the time of screening despite maximal medical management) or presence of symptoms due to elevated blood pressure at the time of screening;
vi. Grade 2 edema of any kind (generalized, pitting, or peripheral); or
vii. Diagnosis of Addison's disease

## 4.4 Patients or Partners of Patients of 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 and its combination partner.

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

Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchiectomy, or with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

Female partners are considered to be of childbearing potential unless one 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; or
- 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.

## 4.5 Compliance with Inclusion/Exclusion Criteria

All inclusion/exclusion criteria must be met for the prospective participant to enroll. Neither the investigator nor the sponsor/designee, may allow a prospective participant who has not met the inclusion/exclusion criteria to enter the study.

# 5 STUDY TREATMENT(S)

This section describes the treatments of rucaparib and combination drugs across all treatment arms.

## 5.1 Description of Investigational Product(s) and Storage

### 5.1.1 Rucaparib

Rucaparib camsylate (also known as CO-338) is an oral formulation. A brief description of rucaparib is provided below with details in the Pharmacy Manual.

**Table 5-1. Description of Rucaparib**

| | |
|---|---|
| Drug Name: | RUBRACA |
| INN: | Rucaparib |
| Formulation: | 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: | 15–30°C (59-86°F) |

### 5.1.2 Enzalutamide

Enzalutamide is an oral formulation. A brief description of enzalutamide is provided below with details in the Pharmacy Manual.

**Table 5-2. Description of Enzalutamide**

| | | |
|---|---|---|
| Drug Name: | XTANDI | |
| INN: | Enzalutamide | |
| Formulation: | 40 mg enzalutamide as white to off-white oblong soft gelatin capsules imprinted with “ENZ” in black ink on one side. | |
| How Supplied: | Bottles of 120 capsules | Cartons of 112 capsules |
| Storage Conditions: | 20-25°C (68-77°F) | < 25°C (< 77°F) |

### 5.1.3 Abiraterone Acetate

Abiraterone acetate is an oral formulation. A brief description of abiraterone is provided below with details in the Pharmacy Manual.

**Table 5-3. Description of Abiraterone Acetate**

| | |
|---|---|
| Drug Name: | Abiraterone |
| INN: | Abiraterone acetate |
| Formulation: | 500 mg film-coated tablets, 250 mg uncoated tablets |
| How Supplied: | Abiraterone 500 mg film-coated tablets are supplied in high-density polyethylene bottles of 60 tablets<br>Abiraterone 250 mg tablets are supplied in high-density polyethylene bottles of 120 tablets |
| Storage Conditions: | 20-25°C (68-77°F) |

## 5.2 Packaging and Labeling

Study drug containers will be labeled according to national regulations for investigational products. Where accepted, the expiry date will not appear on the labels, but will be controlled by the use of an Interactive Web Response System (IWRS).

Details with respect to packaging and labeling of all study drugs are described in the Pharmacy Manual.

### 5.2.1 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° and 30°C (59° and 86°F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle in all treatment arms, including a small overage. One exception is for the 1-week PK run-in period of each arm (both dose escalation and expansion phases) wherein patients will receive enough rucaparib for that time period.

### 5.2.2 Enzalutamide

Enzalutamide is provided in bottles of 120 capsules or cartons of 112 capsules of 40 mg each. The number of containers dispensed to patients will be sufficient to supply 28 days of treatment per cycle, including a small overage.

### 5.2.3 Abiraterone Acetate

Abiraterone acetate are provided in HDPE bottles of 60 × 500 mg tablets or 120 × 250 mg tablets. Abiraterone acetate tablets should be stored in the provided containers between 15° and 30°C (59° and 86°F). Patients will be dispensed one or more strengths depending on their current dose of abiraterone. The number of bottles of each strength dispensed will be sufficient to supply 28 days of treatment per cycle in Arm B, including a small overage.

## 5.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; the investigational products will not be blinded or masked. Patients enrolled will receive rucaparib with the combination drug in a specified treatment arm.

## 5.4 Method of Assigning Patients to Treatment Groups

No randomization is planned for this study. After confirming that a patient fulfills eligibility criteria, the investigator or his/her delegate will enroll the patient into one of the study arms (in either the PK assessment phase or the expansion phase). If a patient appears to be eligible for more than one treatment arm that is open to enrollment, the investigator will be responsible for selecting the most appropriate treatment arm for the patient. However, enrollment into Arm A will be prioritized over Arm B until the objectives for Arm A have been achieved.

## 5.5 Preparation and Administration of Protocol-specified Treatment

Treatment will begin on Day 1 of the run-in period with rucaparib prior to Cycle 1. Patients will be provided a sufficient quantity of rucaparib to last until Day 1 of the next treatment cycle. The assigned combination drug will be dispensed on Cycle 1 Day 1, to last until Day 1 of the next treatment cycle. Patients will be instructed to bring their study drug tablets/capsules and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

If a patient vomits after dosing, the dose will not be made up; the patient will take their next dose at the regularly scheduled interval.

Refer to the Pharmacy Manual for additional information.

### 5.5.1 Rucaparib

For the PK assessment phase of each treatment arm, rucaparib will be administered orally BID at the dose level specified by the dose cohort to which the patient is enrolled.

For the expansion phase of each treatment arm, rucaparib will be administered orally at the combination dose chosen for further exploration. As rucaparib is administered BID, the dose should be administered as close to 12 hours apart as possible, preferably at the same times every day with at least 8 ounces (240 mL) of water starting on Study Day 1 (start of the run-in period). Rucaparib tablets should be swallowed whole without crushing or chewing.

Food has no clinically meaningful effect on rucaparib PK, thus rucaparib tablets may be taken with or without food. In Arm A, there is no food restriction for study drug administration. However, in Arm B, abiraterone acetate and rucaparib should be taken at the same time in the morning on an empty stomach (ie, at least 1 hour before or 2 hours after a meal) to avoid food effect on abiraterone PK.

Rucaparib will be provided as 200, 250, and 300 mg [as free base] dose strength tablets (Section 5.1.1).

### 5.5.2 Enzalutamide

Enzalutamide starting dose will be the full approved dose for mCRPC patients: 160 mg (4 × 40 mg capsules) QD in both the PK assessment phase and the expansion phase in Arm A. Patients receiving enzalutamide should also take GnRH analog concurrently or should have had bilateral orchiectomy. Patients who have not had a bilateral orchiectomy should continue the GnRH analog they were taking prior to enrolling into this study.

Enzalutamide should be dosed together with the rucaparib morning dose and at approximately the same time every day starting on Cycle 1 Day 1. Enzalutamide and rucaparib may be taken with or without food. The enzalutamide capsules should be swallowed whole without crushing or chewing.

Enzalutamide will be provided as 40 mg dose strength capsules (Section 5.1.2).

### 5.5.3 Abiraterone Acetate

Abiraterone acetate starting dose will be the full approved dose for mCRPC patients: 1,000 mg (2 × 500 mg tablets) QD in both the PK assessment phase and the expansion phase in Arm B. Abiraterone acetate must be taken together with prednisone 5 mg orally BID. Patients receiving abiraterone should also take GnRH analog concurrently or should have had bilateral orchiectomy. Patients who have not had a bilateral orchiectomy should continue the GnRH analog they were taking prior to enrolling into this study.

Abiraterone acetate should be dosed together with the rucaparib morning dose and at approximately the same time every day starting on Cycle 1 Day 1. Abiraterone acetate and rucaparib must be taken on an empty stomach (at least 1 hour before or 2 hours after a meal). The abiraterone acetate tablets should be swallowed whole without crushing or chewing.

Abiraterone acetate will be provided as 250 and 500 mg dose strength tablets (Section 5.1.3).

## 5.6 Dose-Limiting Toxicities

A DLT is defined according to criteria specified below and assessed by the investigator, based on toxicity grade (according to the NCI CTCAE v5.0), clinical significance, and possible relationship to the study drug combination (refer to Section 8.7.4 for consideration of causal relationship). The toxicity should not be a recognized adverse effect of enzalutamide, abiraterone or prednisone/prednisolone and/or attributable to mCRPC or mCRPC-related processes under investigation.

The DLT-evaluation period for the determination of dose escalation is the first 2 cycles of rucaparib combination treatment (56 days) for Arm A and the first cycle of rucaparib combination treatment (28 days) for Arm B.

DLTs are defined as:

- Grade 3 or greater febrile neutropenia (ie, fever > 38.3°C with ANC < $1.0 \times 10^9$/L) of any duration or Grade 4 neutropenia lasting more than 7 days despite granulocyte-colony stimulating factor (GCSF) administration;
- Grade 3 thrombocytopenia (platelets < $50 \times 10^9$/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < $25 \times 10^9$/L) ≥ 5 days duration;
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated);
- Any nonhematological AE ≥ Grade 3, with the exception of:
  - Nausea, vomiting, and diarrhea well controlled by systemic medication and with duration ≤ 72 hours;
  - Fatigue;
  - Grade 3 ALT or AST not accompanied by concomitant increase in total bilirubin above the ULN. Note: any Grade 4 ALT/AST is a DLT;
  - Grade 3 arthralgia treated with non-steroidal anti-inflammatory drug(s) (or equivalent) that resolves to ≤ Grade 2 within 14 days;

- Alopecia of any grade.

- Grade 3 QTc prolongation (average QTc ≥ 501 ms; > 60 ms change from baseline, over 3 consecutive assessments) or Grade 4 QTc prolongation (Torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) (Specific to Arm B).

## 5.7 Definition of DLT-evaluable Patient

For Arm A of the study, in order to be considered evaluable for dose escalation/de-escalation decisions, a patient must have received at least 70% of the scheduled doses of both rucaparib and enzalutamide and completed 2 cycles of treatment or have experienced a DLT in either Cycle 1 or Cycle 2. If a patient withdraws from the study without having met either of these criteria, then an additional patient will be enrolled in that cohort; however, safety data, including AEs for that patient will also be considered in dose escalation decisions.

For Arm B of the study, in order to be considered evaluable for dose escalation/de-escalation decisions, a patient must have received at least 80% of the scheduled doses of both rucaparib and abiraterone and completed Cycle 1 of treatment or have experienced a DLT in Cycle 1. If a patient withdraws from the study without having met either of these criteria, then an additional patient will be enrolled in that cohort; however, safety data, including AEs for that patient will also be considered in dose escalation decisions.

## 5.8 Dose Modifications of Protocol-specified Treatment

### 5.8.1 Rucaparib Dose Modification Criteria

Doses of rucaparib may be interrupted or delayed for toxicity and other protocol-specified criteria. Dose reductions are permitted for rucaparib. The assessment for delay or discontinuation should be made separately for rucaparib and its combination partner; however, if toxicity is considered related to all study drugs or if the investigator is unable to determine which study drug is the cause of the AE, then all study drugs in the combination should be delayed and/or discontinued. Treatment may be discontinued due to withdrawal of consent, unacceptable toxicity, disease progression or termination of the study, whichever occurs first.

Dose modification and retreatment of rucaparib are to be based on the criteria presented in Table 5-4.

## Table 5-4. Dose Modification Criteria for Rucaparib

| Adverse Event including Laboratory Abnormalities | Severity (CTCAE Grade) | Rucaparib | | |
|---|---|---|---|---|
| | | Treatment Interruption | Retreatment | Dose Modification |
| Adverse event or laboratory abnormality | 1 or 2 | None[a] | N/A | None |
| Adverse event[b] | 3 or 4 | Hold dose | ≤ Grade 2 | **1st occurrence:** Same dose<br>**2nd or 3rd occurrence of same AE:** Reduce dose[c] |
| ALT/AST elevation (in the absence of other signs of liver dysfunction) | 3 | Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 × ULN; monitor LFTs weekly;<br>Hold if levels do not decline within 2 weeks or if levels increase | ≤ Grade 2 | **1st occurrence:** Same dose<br>**2nd occurrence or more of same AE:** Reduce dose[c] |
| ALT/AST elevation | 4 | Hold | ≤ Grade 2 | Reduce dose; monitor LFTs weekly for 3 weeks (Section 5.8.2) |
| ALT or AST elevations (> 3 × ULN)<br>AND total bilirubin (> 2 × ULN) - suspected DILI (Section 8.9) | N/A | Hold[d];<br>Monitor LFTs weekly | ≤ Grade 1 (or baseline) | Subject to investigation: reduce dose[c]<br>If DILI is confirmed, treatment should be permanently discontinued |
| Anemia | ≥ 3 | Hold dose[e] | ≤ Grade 2 | Same or reduced dose[a, c] |

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; INR = international normalized ratio; LFT = liver functions test; N/A = not applicable; ULN = upper limit of normal.

[a] At the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity that is attributed to rucaparib and not adequately controlled by concomitant medications and/or supportive care.

[b] Exceptions include Grade 3 or 4 nausea, vomiting, or diarrhea adequately controlled with systemic anti-emetic/antidiarrheal medication administered in standard doses according to institutional guidelines.

[c] For dose reductions, see Section 5.8.2.

[d] Evaluate patient for the presence of confounding factors, including malignant disease in the liver, co-administration 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 INR should be implemented as indicated. If no alternative cause is identified, study drugs must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

[e] If anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusions occurs, then weekly complete blood counts should be performed until resolution of the event. If after 42 days of interruption and anemia has not improved to CTCAE Grade ≤ 1, the patient should be referred to hematologist and analysis of the bone marrow with cytogenetic studies and recommended according to standard practice. 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).

#### 5.8.1.1 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 computed tomography [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 judgment 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 8.3 and 8.7 of the protocol for additional information regarding classification and reporting of pneumonitis (and similar events) as an AESI.

### 5.8.2 Rucaparib Dose Modification Steps

Dose reduction steps are presented in Table 5-5. Dose reduction steps from a starting dose of greater than 600 mg BID will be determined and agreed upon by the Dose Review Committee, based on the starting dose, exposure of rucaparib achieved and toxicities observed in prior dose level cohort(s).

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

If rucaparib PK is decreased by 25-50% due to interactions with its combination partner, (particularly in Arm A), it may be necessary to escalate the dose of rucaparib from 600 mg BID to a maximum of 1,000 mg BID. The increase in rucaparib dose will be determined by exposure observed in the prior cohort of patients.

Dose modifications (ie, interruption, reduction, and/or re-escalation) must be recorded for each patient in the appropriate section of the eCRF (see Section 10.5).

**Table 5-5. Rucaparib Dose Reduction Steps**

| Starting Dose | 600 mg BID |
|---|---|
| Dose Level – 1 | 500 mg BID |
| Dose Level – 2 | 400 mg BID |
| Dose Level – 3[a] | 300 mg BID |

Abbreviation: BID = twice a day.

[a] Consult with sponsor's medical monitor before reducing the dose to this level.

### 5.8.3 Enzalutamide or Abiraterone Dose Modification

Dose reductions will not be permitted for enzalutamide, abiraterone or prednisone in the PK assessment phase, unless the patient experiences a DLT. For treatment interruptions or dose modifications necessary for either enzalutamide or abiraterone for patients enrolled and treated in the PK assessment portion of the study and who have completed the DLT assessment period or for patients enrolled into the expansion phase, refer to the applicable prescribing information for further details and for any additional restrictions or cautions required due to the administration of enzalutamide, abiraterone or prednisone.

Arm A: Discontinuation of enzalutamide may be warranted (refer to prescribing information) if the patient exhibits the following symptoms/syndromes: seizure, posterior reverse encephalopathy syndrome, hypersensitivity or ischemic heart disease.

Arm B: Discontinuation of abiraterone and/or modification of abiraterone may be warranted (refer to the prescribing information) if the patient exhibits symptoms of mineralocorticoid excess, adrenocortical insufficiency or hepatotoxicity.

## 5.9 Treatment Compliance

As of the implementation of Protocol Amendment 2, the requirement to use drug dosing diaries will be discontinued, and compliance and dosing data are no longer required to be entered in the eCRF (see Section 10.5).

Study site personnel will review dosing information with the patient (or legally authorized representative, where acceptable) 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, where acceptable according to local regulations) will be instructed to keep all unused containers (empty, partially used, and/or unopened) for accountability at scheduled clinic visits. Documentation of dosing will be recorded in a study-specific dosing diary provided by the sponsor (or designee). Dosing noncompliance is defined as a patient missing > 14 days of study drug within a cycle for 2 consecutive cycles for reasons other than toxicity. The sponsor may require patients meeting noncompliance criteria to discontinue study treatment.

A compliance check and tablet count will be performed by study site personnel during clinic visits. Study site personnel will record compliance information on the eCRF (see Section 10.5). Additional details regarding study drug dispensation and return can be found in the Pharmacy Manual.

Every effort should be made to ensure patients return all study drug containers/unused study drugs at the end of each cycle of treatment. Study site personnel should conduct a verbal review of dosing with the patient and document the discussion in the patient's medical record. This documentation may serve as source documentation for entering dosing data on the appropriate eCRF (see Section 10.5).

## 5.10 Accountability of Protocol-specified Treatment

Study site personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation for study drugs provided by the sponsor. The IWRS will be used to manage study drug inventory at all sites. To function properly, the system will require real-time entry of study drug receipt, dispensation, destruction, etc. by study site personnel.

The site is responsible for the return or destruction of study drug supplied by the sponsor, as required. Authorization for on-site destruction of study drug that has not been dispensed to a patient (eg, expired study drug), must be requested from the sponsor prior to destruction. All study drug containers must be accounted for prior to their destruction at the study site, according to institutional procedures for disposal of hazardous materials. Unused and returned study drug product and containers should be destroyed on-site if possible. If on-site destruction is not possible, supply should be returned to the drug depot, following the sponsor's instructions.

During the study and at completion of the study, the number of study drug units and containers received, dispensed, returned, and destroyed must be recorded and reconciled. Additional details regarding study drug accountability can be found in the Pharmacy Manual.

## 5.11 Investigational Treatment Beyond Disease Progression

Patients will receive study drugs until confirmed radiologic disease progression as assessed by investigator using mRECIST/PCWG3 criteria, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other anticancer therapy, or termination of the study (refer to Section 10.6).

If a patient receiving study drugs has met criteria for confirmed radiologic disease progression by mRECIST/PCWG3, but the patient continues to derive clinical benefit per the investigator, then continuation of study drug(s) may be permitted upon discussion with the medical monitor. In such cases, the documented decision to continue will be made jointly between the investigator and the sponsor (or designee), it must be documented in the patient's chart, and the patient must provide consent within a reasonable timeframe of the documented decision to continue study treatment. Clinical scenarios where continuation of study drugs after radiographic progression may be considered include, but are not limited to:

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 study drug(s) will continue to have all protocol-required assessments as described in Section 7.

# 6 PRIOR AND CONCOMITANT THERAPY

As of the implementation of Protocol Amendment 2, it is no longer required to document procedures and medications used during the study in the eCRF (see Section 10.5).

## 6.1 Supportive Care

During the study, supportive care (eg, anti-emetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures.

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.

## 6.2 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, with the exception of palliative radiotherapy and hormonal treatment, such as GnRH therapy. Prior treatment with such excluded anticancer therapies must have been completed > 14 days prior to the first dose of study drug or as specified in the treatment arm-specific inclusion/exclusion criteria (Section 4.2 and Section 4.3, respectively).

Any botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care are prohibited (except those prescribed as supportive care by a health care professional as per Section 6.1).

## 6.3 Radiotherapy

Palliative radiotherapy on lesions not considered target lesions for tumor evaluation is permitted during the study. Treatment with study drug should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation related toxicity.

## 6.4 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

At the steady state following treatment with 600 mg rucaparib BID, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Refer to the

rucaparib IB, Contraindications and Precautions, for caution when co-administering medicinal products that are CYP substrates.

Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. To assess the effect of enzalutamide on rucaparib PK, no other strong or moderate CYP3A inhibitors or inducers are allowed.

In addition, the following rules should be followed in specific study arms:

- Arm A: Enzalutamide is a substrate of CYP2C8 and CYP3A4. Concomitant strong CYP2C8 inhibitors, strong CYP3A4 inducers are prohibited. Enzalutamide is a strong CYP3A4 inducer, and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use with drugs that are sensitive substrates of CYP3A4, CYP2C9, or CYP2C19 should be avoided.
- Arm B: Concomitant strong CYP3A4 inducers and sensitive CYP2D6 substrates are prohibited.

Refer to Appendix 3 for examples of sensitive CYP substrates and refer to Appendix 4 for examples of CYP inhibitors and inducers.

## 6.5 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 and enzalutamide is a moderate CYP2C9 inducer. Caution should be exercised particularly in Arm A, for patients receiving rucaparib or enzalutamide with concomitant warfarin (Coumadin). Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

Direct oral anticoagulants (eg, apixaban, rivaroxaban, and dabigatran) have elimination mediated by CYP3A4 and/or P-gp. As enzalutamide is a strong CYP3A4 inducer in vivo, and enzalutamide and N-desmethyl enzalutamide are P-gp inhibitors in vitro, concomitant administration with enzalutamide may result in altered exposures of these anticoagulants. If such anticoagulants have to be used, monitor INR regularly per standard clinical practice.

## 6.6 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on patient attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each patient. Oral and/or intravenous (IV) contrast should be used whenever possible and appropriate, and rectal contrast should only be considered in patients with peritoneal disease. Imaging contraindications and contrast risks should be considered in this assessment. Patients with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to magnetic resonance imaging (MRI), patients with severe renal insufficiency (ie, estimated GFR < 30 mL/min) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this patient population. In addition, patients should not get MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual patient in this study rests with the site radiologist, the investigator and the standard set by the local IRB.

## 6.7 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 (see Section 10.5). 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 (see Section 10.5).

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 after starting rucaparib and then regularly per standard clinical practice.

In vitro, rucaparib is a potent inhibitor of MATE-1 and MATE-2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease renal elimination and liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

Abiraterone is a weak CYP2C8 inhibitor in vivo. In vitro, abiraterone and its metabolites inhibit organic anion transporter (OAT) OATP1B1. Use caution if sensitive CYP2C8 substrate drugs or OATP1B1 substrate drugs need to be used concomitantly with study drugs.

Refer to the rucaparib IB and to the enzalutamide or abiraterone prescribing information for additional information.

## 6.8 General Restrictions

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 STUDY PROCEDURES AND METHODS

## 7.1 Schedule of Assessments

**Table 7-1 summarizes the procedures and assessments to be performed for all patients remaining on study drug or in follow-up as of the implementation of Protocol Amendment 2. The revised evaluations should commence immediately after the patient has provided appropriate informed consent, maintaining previous treatment cycle and day sequence.**

The purpose of the revised SOA is to allow patients who continue to benefit from treatment with the combination to continue receiving study drugs, but to reduce the number of assessments required at study visits (including at the end of treatment and follow-up assessments), while maintaining an appropriate level of safety monitoring.

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

Both arms will start with a 1-week run-in period with rucaparib alone, followed by continuous 28-days treatment cycles of rucaparib and the combination drug. The DLT period in Arm A will be across Cycles 1 and 2, and for Arm B will be across Cycle 1.

Food restriction must be followed for the morning doses of abiraterone acetate and rucaparib. The doses must be taken on an empty stomach at least 1 hour before or 2 hours after a meal. There is no food restriction in Arm A and evening doses of rucaparib in Arm B.

Table 7-2 summarizes the PK sample collection schedule for all patients in Arm A and Arm B. Predose PK samples will be collected at the specified timepoints.

## Table 7-1. Revised Schedule of Assessments as of the Implementation of Protocol Amendment 2

| Procedure[a] | Treatment Phase (± 3 days) Cycle X Day 1 | Post-Treatment Phase | |
|---|---|---|---|
| | | End of Treatment (± 3 days after last dose) | 28-Day Follow-up |
| Adverse Events[b] | The investigator should monitor and educate patients on possible AEs observed with the treatment combination | | X |
| Complete Blood Count | Monthly assessments advised | | |
| Clinical Chemistry, Urinalysis, Vital Signs | Local standard of care practices per investigator | | |
| Disease Assessments (Imaging/PSA) | Local standard of care practices per investigator | | |
| Arm A: Rucaparib Dispensation/Administration/Accountability | X | X | |
| Arm A: Enzalutamide Dispensation/Administration/Accountability | X | X | |

Abbreviations: AE = adverse event, AESI = adverse event of special interest, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome, PSA = prostate-specific antigen, PV = pharmacovigilance, SAE = serious adverse event.

[a] Treatment cycles are 28 days. Unless otherwise specified, all assessments are to be completed within ± 3 days of scheduled time point.

[b] AEs will be monitored, but only SAEs/AESIs will be reported through 28 days after the last dose of study drug. Ongoing SAEs, AESIs and Grade 3/4 treatment-related AEs will be followed until resolution, stabilization, or lost to follow-up. SAEs/AESIs will be collected per Clovis PV guidelines and reported in the Clovis PV database through the 28-day Follow-up Visit after the last dose of study drug. 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 assessed as potentially related to study drug, and AESIs of MDS and AML irrespective of causality, will be reported.

Note: Treatment Arm B was not activated.

**Table 7-2. Pharmacokinetic Sample Collections in Treatment Arm A and Arm B (PK Assessment and Expansion)**

| Cycle | Study Visit | Rucaparib PK | Combination Drug[a] PK |
|---|---|---|---|
| **Rucaparib Run-In** | D6, D7 | Predose[b] | N/A |
| **Cycle 1** | D1, D8, D15, D22 | Predose[b] | Predose[b] |
| **Cycle 2** | D1 | Predose[b] | Predose[b] |
| **Cycle 2 (Arm A only)** | D8, D15, D22 | Predose[b] | Predose[b] |
| **Cycles 3, 4, 6, and 8** | D1 | Predose[b] | Predose[b] |

Abbreviations: D = day; N/A = not applicable; PK = pharmacokinetics.

[a] Arm A, enzalutamide and N-desmethyl enzalutamide; Arm B, abiraterone

[b] Predose refers to collection prior to the morning dose of both rucaparib and the combination drug. The predose PK sample should be collected within 30 minutes before taking the morning dose of study drugs. Special attention is required for Arm B where rucaparib and abiraterone acetate should be taken on an empty stomach (at least 1 hour before or 2 hours after a meal); the predose PK samples should be collected at a time in the morning with assurance that the drugs can be administered within 30 minutes after PK sampling.

Notes: Collection of the actual time(s) of dose administration and PK sampling is essential for PK analysis. Refer to the Laboratory Manual for details on sample handling and processing.

## 7.2 Informed Consent Process

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, informed consent must be obtained from each potential patient (or legally authorized representative) prior to any study activities. The information on the IRB-approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand. A separate consent form may be used for tissue testing.

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

## 7.3 Methods of Data Collection

As of the implementation of Protocol Amendment 2, it is no longer required to record data in the eCRF (see Section 10.5); however, SAEs and AESIs will be reported to Clovis PV as described in Section 8.7.

### 7.3.1 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 due to a protocol-mandated procedure, should be recorded on the Medical History eCRF.

The patient's entire relevant oncology history will be collected on the appropriate eCRF including date of diagnosis for prostate cancer, prior surgeries/treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, progression-free interval after last platinum regimen (if applicable), radiology reports, and status (germline or somatic – if known) of deleterious mutation in BRCA1/2 or other HRR gene.

### 7.3.2 Prior and Concomitant Medication Assessments

Medications being used by the patient will be recorded as prior/concomitant medications during screening.

As of Protocol Amendment 2, information on concomitant medications will no longer be collected.

### 7.3.3 Efficacy Evaluations

#### 7.3.3.1 Disease/Tumor Assessments

Disease/tumor assessments will be performed according to local standard of care per investigator.

Tumor response will be interpreted using mRECIST/PCWG3 criteria (Appendix 1).

#### 7.3.3.2 Tumor Markers

Blood samples to assess PSA will be collected according to local standard of care per investigator, and as clinically indicated. PSA will be measured by a local laboratory.

### 7.3.4 Safety Evaluations

#### 7.3.4.1 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 screening period, unless otherwise required by local regulations, AEs/SAEs related to protocol-mandated procedures will be reported. As of the implementation of Protocol Amendment 2, during and at the end of treatment, AEs will be monitored but only SAEs/AESIs will be reported through 28 days after the last dose of study drug. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution, stabilization, or lost to follow-up. After the 28-day window, only SAEs assessed as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database.

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 similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28 days after the last dose of study drug). After the 28-day Follow-up Visit, only **serious** pneumonitis or similar events assessed as **potentially related to study drug** should be reported per Clovis Oncology PV requirements.

In the time after informed consent is provided but before rucaparib is administered, AEs/SAEs are to be recorded if they are the result of a study-related procedure. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (v5) and recorded on the eCRF (see Section 10.5).

Complete details for monitoring AEs (inclusive of SAEs and AESIs), including the definition of drug-related AEs, are provided in Section 8.

#### 7.3.4.2 Clinical Laboratory Investigations

As of the implementation of Protocol Amendment 2, monthly hematology assessment, consisting of a complete blood count, is advised. Clinical chemistry assessments will be performed according to local standard of care per investigator.

As of the implementation of Protocol Amendment 2, urinalysis will be performed according to local standard of care per investigator.

#### 7.3.4.3 Vital Signs

As of the implementation of Protocol Amendment 2, vital signs will be performed according to local standard of care per investigator.

#### 7.3.4.4 12-Lead Electrocardiograms

As of the implementation of Protocol Amendment 2, ECGs will no longer be required.

#### 7.3.4.5 Physical Examinations, Body Weight and Height

As of the implementation of Protocol Amendment 2, physical examinations, body height and weight assessments will no longer be required.

#### 7.3.4.6 ECOG Performance Status

As of the implementation of Protocol Amendment 2, ECOG performance status assessments will no longer be required.

### 7.3.5 Pharmacokinetic Assessments

As of the implementation of Protocol Amendment 2, the PK assessment phase is complete and PK samples are no longer being collected.

PK samples will be collected according to Table 7-2.

In Arm A, patients will receive treatment of rucaparib for 1 week (Run-In Days 1-7), followed by treatments of enzalutamide and rucaparib in 28-day cycles. Plasma PK samples will be collected prior to the morning doses in on Run-In Days 6 and 7 during the run-in period, and on Days 1, 8, 15 and 22 of Cycles 1 and 2, and on Day 1 of Cycles 3, 4, 6 and 8. The morning dose should be approximately 24 hours after the previous morning doses of enzalutamide and rucaparib, and approximately 12 hours before the previous evening dose of rucaparib. If the start of the next treatment cycle is delayed, the PK sample should still be collected during this visit instead of on Day 1 of the delayed start of the next treatment cycle. Concentrations of enzalutamide, its metabolite N-desmethyl enzalutamide, rucaparib, and its metabolite M324 will be determined using validated assays.

In Arm B, patients will receive treatment of rucaparib for 1 week (Run-In Days 1-7), followed by treatments of abiraterone and rucaparib in 28-day cycles. Plasma PK samples will be collected prior to the morning doses on Run-In Days 6 and 7 during the run-in period, on Days 1, 8, 15 and 22 of Cycle 1, as well as on Day 1 of Cycles 2, 3, 4, 6, and 8. The morning dose should be approximately 24 hours after the previous morning doses of abiraterone acetate and rucaparib, and approximately 12 hours before the previous evening dose of rucaparib. If the start of the next treatment cycle is delayed, the PK sample should still be collected during this visit instead of on Day 1 of the delayed start of the next treatment cycle. Concentrations of abiraterone, rucaparib and its metabolite M324 will be determined using validated assays.

Refer to the Laboratory Manual for sample collection, handling, and storage details for PK samples.

### 7.3.6 Biomarker Analyses

The biomarker samples and analyses are described below. The Laboratory Manual will include details of the sampling methods, number of samples to be collected, processing, handling, and storage.

As of the implementation of Protocol Amendment 2, the collection of blood samples for biomarker analysis has been completed and no additional samples will be collected.

#### 7.3.6.1 Formalin-fixed Paraffin-embedded Tumor Tissue or Fresh Tumor Biopsy

Optional archival formalin-fixed paraffin-embedded (FFPE) tumor tissue or metastatic biopsy sample (preferred) will be collected from patients. Next-generation sequencing (NGS) will be performed on these samples, and the relationship between genomic alterations and signatures to clinical outcomes from treatment will be assessed.

#### 7.3.6.2 Optional Tumor Biopsy

As of the implementation of Protocol Amendment 2, post-treatment tumor biopsies will no longer be collected.

#### 7.3.6.3 Blood Sample for Plasma ctDNA Analyses

Blood samples for plasma ctDNA analyses will be collected during screening, before dosing with rucaparib on the first run-in day, and on Day 1 of Cycle 2 during combination treatment. These samples will be used for genomic profiling to assess alterations in genes that may be associated with response and resistance to rucaparib in combination with AR-directed therapy.

#### 7.3.6.4 Blood Sample for Pharmacogenomics Analyses

Blood samples for pharmacogenomics analyses will be collected at Study Day 1 of the run-in period from all patients. If the pharmacogenomics sample is missed, it may be collected during a later cycle (ie, Cycle 2 or later). Genomic DNA will be extracted from the cellular portion of these blood samples analyzed to determine whether the BRCA1/2 mutation or other HRR gene mutation is germline or somatic prior to final data analysis. Additionally, polymorphisms of absorption, distribution, metabolism and excretion (ADME)-related genes relevant to the DDI analysis may be explored per sponsor's request.

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 may be made available to the investigator provided the results are generated from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

#### 7.3.6.5 Additional Research

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

# 8 ADVERSE EVENT MANAGEMENT

As of the implementation of Protocol Amendment 2, it is no longer required to record AEs in the eCRF (see Section 10.5); however, SAEs and AESIs will be reported to Clovis PV as described in Section 8.7.

## 8.1 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, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF (see Section 10.5) 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, instead of the physical examination eCRF [see Section 10.5], which is reserved for physical signs or findings).

## 8.2 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 study drug through 28 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect
- Is an important medical event – Important medical events may not result in death, are not life-threatening, or do not require hospitalization but 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.

## 8.3 Definition of an Adverse Event of Special Interest

Adverse events 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 study 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 8.7 for reporting instructions). Details on the AESIs for either enzalutamide or abiraterone can be found in the prescribing instructions.

## 8.4 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 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 (see Section 10.5). The accompanying SAE should be reported and overdose should be described in the report;
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE or SAE; or
- Events that meet the SAE criteria (as outlined in Section 8.2) and occur after informed consent but before the first dose of study drug, which are considered unrelated to protocol-mandated screening procedures.

## 8.5 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 laboratory values within the normal range will require similar judgment.

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

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

## 8.6 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.

All pregnancies 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.

## 8.7 Reporting 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 study drug, unless due to a protocol-mandated procedure, are to be recorded on the Medical History eCRF (see Section 10.5); however, during this time if the event is serious and related to a protocol-mandated procedure it is to be reported as an SAE. As of the implementation of Protocol Amendment 2, during and at the end of treatment, AEs will be monitored but only SAEs/AESIs will be reported through 28 days after the last dose of study drug.

After the 28-day Follow-up Visit, only SAEs assessed as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database.

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 similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28 days after the last dose of study drug). After the 28-day Follow-up Visit, only **serious** pneumonitis or similar events assessed as **potentially related to study drug** should be reported per Clovis Oncology PV requirements.

Information on the follow-up of AEs, SAEs and AESIs is provided in Section 8.8.

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 the investigational drug, 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 study drug, whether or not related to study drug, 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.

### 8.7.1 Onset Date of Adverse Events

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

### 8.7.2 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.

### 8.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, v5 grading scale.[39]

"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 transient and do not interfere with the patient's daily activities,
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities,
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required,
- Life-threatening events require urgent intervention to prevent death, or
- Fatal events are those events that lead to the patient's death.

### 8.7.4 Causal Relationship of Adverse Events to Study Drug

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, co-existing disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, and dechallenge or rechallenge with the study drug (Table 8-1).

**Table 8-1. Causal Relationship of Adverse Events to Study Drug**

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

### 8.7.5 Outcome and Action Taken

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

**Action Taken with Study Drug (note all that apply)**

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

**Outcome**

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving

- Ongoing
- Death
- Lost to follow-up

## 8.8 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 assessed as potentially related to study drug and all AESIs of MDS and AML, irrespective of causality, should be reported.

- AESIs of pneumonitis or similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the 28-day Follow-up Visit (ie, 28 days after the last dose of study drug). After the 28-day Follow-up Visit, only **serious** pneumonitis or similar events assessed as **potentially related to study drug** should be reported per Clovis Oncology PV requirements.

## 8.9 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,[32] must be reported as SAEs (see Section 8.7 for reporting details).

Potential drug-induced liver injury is defined as:

1. ALT or AST elevation > 3 × ULN
   AND
2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP),
   AND
3. No other immediately apparent possible causes of ALT/AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## 8.10 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 US FDA, according to 21 Code of Federal Regulations (CFR) 312.32. 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.

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

# 9 STATISTICAL METHODS

**General Considerations**

Quantitative variables will 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 (StD), median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

All data will be used to their maximum possible extent but without any imputations for missing data. 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, v 9.3 or higher. Further details around the statistical analyses planned in this study will be outlined in the statistical analysis plan (SAP). Changes to or deviations from the SAP will be described in the clinical study report (CSR).

## 9.1 Determination of Sample Size

The total enrollment planned is up to 60 evaluable patients (30 in Arm A and 30 in Arm B).

The overall sample size in the PK assessment phase of each arm depends on the occurrence of safety findings, specifically DLTs, observed at the different dose regimens. It is anticipated that a minimum of 6 and maximum of 18 patients will be enrolled, unless additional patients are required to be enrolled, due to some patients not being evaluable for DLT assessment.

The Dose Expansion phase of each arm will enroll up to 12 additional patients to evaluate the optimal dose combination for each treatment arm.

A total of 18 patients at the recommended combination dose in each treatment arm is anticipated to provide adequate PK information (in addition to safety and tolerability) for each combination. Assuming an intra-subject PK variability of 40%, N = 18 patients would be sufficient for the point estimate of the geometric ratio of trough concentration (ie, concentration before the next dose is administered [$C_{trough}$]) of rucaparib with and without co-administration of one of the combination drugs to fall within 80% and 125% of the true value with 90% confidence. Fewer patients may be enrolled if the PK variability is less than anticipated.

If a patient drops off the study or becomes unevaluable for safety (DLTs), an additional patient may be enrolled.

## 9.2 Analysis Populations

The following analysis populations are defined for the study:

- **Dose-limiting toxicity (DLT)-evaluable Population** – For Arm A, the DLT-evaluable population will consist of all patients who completed at least 70% of the scheduled doses of both rucaparib and enzalutamide and completed Cycles 1 and 2 of treatment, or who experienced a DLT in Cycles 1 or 2. For Arm B, the DLT-evaluable population will consist of all patients who completed at least 80% of the scheduled doses of both rucaparib and enzalutamide and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.
- **Safety Population** – The safety population will consist of all patients who received at least 1 dose of any study drug.
- **Efficacy Population** – The efficacy population will consist of all patients evaluable for response by mRECIST/PCWG3 criteria (ie, PSA response) and could be subdivided into the RECIST-evaluable population and the PSA-evaluable population.
- **Pharmacokinetic (PK) Population** – The PK population will consist of all patients who received at least 1 dose of study drug and had at least 1 measurable concentration.

## 9.3 Patient Disposition

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.

## 9.4 Demographics and Baseline Characteristics

All demographic and baseline characteristics will be summarized for the safety population.

In addition to basic demographic characteristics, 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 characteristics of a deleterious mutation in BRCA1/2 or other HRR gene will also be summarized for patients with these mutations:
  - Status (germline or somatic) of mutation in BRCA1/2 or other HRR gene

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

## 9.5 Efficacy Analysis

The secondary efficacy endpoints will be analyzed by calculating response rates. The ORR is defined as the proportion of patients with a documented and confirmed best overall response of complete response (CR) or partial response (PR) per mRECIST v1.1 as assessed by the investigator. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment at least 4 weeks after initial response.

ORR (confirmed CR+PR) will be summarized with frequencies and percentages, Similar summaries of patients with a best overall response of CR, PR, stable disease (SD), or progressive disease (PD) will be presented. All summaries of response rates will be accompanied by 95% CIs.

PSA response per PCWG3 criteria is a confirmed PSA response (≥ 50% decrease from baseline) as reflected local laboratory measurements. PSA response rate will be summarized along with a 95% CI.

## 9.6 Safety Analyses

All safety analyses will be summarized for the Safety Population.

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

AEs, clinical laboratory results, vital signs, ECG results, ECOG PS, body weight, and concomitant medications/ procedures will be tabulated and summarized.

### 9.6.1 Extent of Exposure

Duration of exposure will be summarized descriptively and categorically. The number and percentage of patients with dose reductions and dose interruptions will be provided.

### 9.6.2 Adverse Events

Adverse events 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 v5.0. TEAEs are defined as AEs with onset date ranging from on or after the date of first dose of study drug until 28 days after the last dose of study drug.

The number and percentage of patients who experienced TEAEs for each System Organ Class (SOC) and Preferred Term (PT) will be presented. Multiple instances of the TEAE in

each SOC and multiple occurrences of the same PT are counted only once per patient. The number and percentage of patients with at least one 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;
- Treatment-related serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study;
- TEAEs resulting in interruption/delay of study drug; and TEAEs resulting in dose reduction of study drug.

The incidence of TEAEs will be summarized by relationship to study drug (rucaparib and/or enzalutamide/abiraterone) 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 for the study drug, 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.

### 9.6.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology and chemistry. The laboratory values will generally be presented in International System of Units (SI). The treatment period will be defined as the time from the first dose of rucaparib to 28 days after the last dose of rucaparib or the last Safety Follow-up Visit, whichever is later. Laboratory values collected during the treatment period will be included in the summary tables. The laboratory values collected after the 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 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 Grade 4 criteria according to CTCAE).

### 9.6.4 Vital Sign Measurements

The treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of drug or the last Safety Follow-up Visit, whichever is later. Vital sign measurements collected during the treatment period will be included in the summary tables. The vital sign measurements collected after the treatment period will only be presented in the data listings.

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

### 9.6.5 Other Safety Measurements

Body weight will be summarized descriptively (N, mean, StD, median, minimum, and maximum). 12-lead electrocardiogram findings and ECOG status will be summarized categorically.

## 9.7 Pharmacokinetic Analysis

Plasma concentrations of rucaparib, its combination drug partner and their metabolite of interest will be determined using validated high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) methods. The $C_{min}$ data of rucaparib, the combination drugs, and metabolites will be reported, and summary statistics be provided.

The effect of combination drug on the PK of rucaparib and M324 will be assessed by comparing their steady-state $C_{min}$ with and without treatment of the combination drug in each arm. The M324-to-rucaparib steady-state $C_{min}$ ratio with and without treatment of the combination drug in each arm will also be determined.

## 9.8 Exploratory Analysis

Genomic alterations detected in blood or tissue samples will be correlated to clinical efficacy of the rucaparib combination treatments.

## 9.9 Interim Analysis

No formal interim analysis is planned.

# 10 STUDY ADMINISTRATION

## 10.1 Regulatory and Ethical Considerations

### 10.1.1 Good Clinical Practice

The study will be conducted in accordance with the protocol and applicable Standard Operating Procedures (SOP); 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)
- EU Directives 2001/20/EC, 2003/94/EC, 2005/28/EC, 536/2014, and
- All applicable local requirements, including 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, 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 noncompliance, the sponsor will promptly notify the regulatory authority.

All potential serious breaches of GCP must be reported to 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 patients in 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 or fraud (eg, loss of medical licensure, debarment).

### 10.1.2 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 study-specific 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 a 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 medical 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).

### 10.1.3 Institutional Review Board or Independent Ethics Committee Approval

This protocol, the IB, and any material to be provided to the patient (such as the ICF, advertisements, Patient Information Sheets (PIS), drug dosing diaries, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB/IEC. This also applies to protocol amendments.

The sponsor will supply relevant data for the investigator to submit the study protocol and additional study documents to the IRB/IEC. The investigator will submit the study protocol for review and approval by an IRB/IEC, according to national law and/or local regulations, and will provide the IRB/IEC with all appropriate materials.

Verification of the IRBs/IECs unconditional approval of the study protocol and the written ICF will be transmitted to the sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review and approval.

No patient will be admitted to the study until appropriate IRB/IEC approval of the study protocol and ICF/PIS have been received, the investigator has obtained the patient's signed and dated ICF/PIS, and the eligibility criteria have been satisfied and confirmed.

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

The IRB/IEC must be informed by the investigator of all subsequent study protocol amendments and of SAEs or suspected unexpected serious adverse reactions (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.

## 10.2 Patient Information and 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 and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The ICF, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IRB/IEC and be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IRB/IEC. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legally authorized representatives [where acceptable according to national law and/or local regulations], if necessary) 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 concerned. Both the patient and the person who explains the study and ICF to the patient will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each study patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

## 10.3 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, not names or, in some regions, initials) according to country regulations should be recorded on any form submitted to the sponsor and the IRB/IEC. The investigator must record all screened and enrolled patients in the eCRF. The investigator must maintain a list where the identity of all study participants can be found, but not intended for use by the sponsor.

The investigator further agrees to take all reasonable precautions to prevent the disclosure of confidential patient information to any unauthorized party or into the public domain. The investigator will notify Clovis Oncology (ithelpdesk@clovisoncology.com) within 24 hours of a security event that impacts or has the potential to impact the confidentiality, integrity, or availability of patient study data.

## 10.4 Study Monitoring

On behalf of the sponsor, a contract research organization (CRO) or contract monitor will contact or 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, and the potential investigator/site are in good standing with respect to previous regulatory compliance, in which case this initial visit maybe waived) and at appropriate intervals during the study until after the last patient is completed.

In accordance with ICH GCP and local regulations, the clinical monitor will periodically review, via direct access, eCRFs, study documents, and medical records (office, clinic, or hospital) for patients enrolled in this study. Monitors will not share patient identifiers with the sponsor. Additionally, the clinical monitor will review and assess research facilities and clinical laboratory facilities associated with the study. Clinical monitoring will be scheduled to occur 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.

Where applicable, if the sponsor or their representatives are not able to come to the study center, patient study data may be reviewed by them remotely, in conformity with the applicable institutional guidance and local regulations. The site staff may place relevant medical records, with personal identifiers removed, into a secure computer system for the sponsor or their representative to view, allow them to view these records during a video conference, and/or provide them direct access to patients' electronic medical records. This review would occur in a manner that protects the confidentiality of study patient data. Whether a patient's medical records are reviewed at the study center or remotely, their identity and medical records will be kept secure during this process. Remote review of patient study data should not be carried out if adequate data protection, including data security and protection of personal data even if pseudonymized, is not ensured. Further details will be provided in the study training materials and/or the clinical monitoring plan.

The investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The purpose of these visits is to allow the clinical monitor an opportunity to verify adherence to the study protocol and assess the completeness, consistency, and accuracy of data entered on the eCRFs and other documents; however, the investigator retains ultimate responsibility for the quality and integrity of data generated by the site. The clinical monitor will confirm all aspects of the study that are essential for human patient protection and safety as well as those related to the validity and reliability of study data.

The investigator will make all source data (ie, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing study patients' relevant source data that are maintained in site records with the information entered on the eCRF (ie, source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs; however, the investigator retains ultimate responsibility for the quality and integrity of data generated by the site.

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. Representatives from the sponsor may also contact and visit the investigators and monitor data during the study.

## 10.5 Case Report Forms and Study Data

**Upon approval of Protocol Amendment 2, collection of data in eCRFs is no longer required as the study database will be locked.**

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 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 and handwritten initials of all individuals delegated responsibility on this study. This "study site personnel and delegation list" must be kept current throughout the study.

Clinical data (including AEs, concomitant medications, and expected adverse reactions 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. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted in the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should 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 and input 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 from the source documents.

## 10.6 Study Termination and Site Closure

The sponsor, the investigator/institution, or IRB/IEC 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.

The sponsor reserves the right to discontinue 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 the study treatment.

If the study 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).

## 10.7 Modification of the Study Protocol

Protocol modifications (ie, 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 IRB/IEC 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 for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines. Protocol deviations are described in Section 10.9.1.

## 10.8 Retention of Study Documents

The study site will maintain a study file, which should contain all documents defined in the ICH E6(R2) Guideline for Good Clinical Practice. The investigator should have control of all essential documents generated by the site. Source documents must be maintained, ALCOA+ documentation practice used. Any changes to source data should be traceable, should not

obscure the original entry, and should 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 ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities 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 10 years after the investigation is discontinued and FDA is notified. No data should be destroyed without the agreement of the sponsor. Copies of original documents should 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 study-related records are no longer needed.

All clinical study information should 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.

## 10.9 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. Patient protection and safety and the reliability of study results are major areas of focus for the procedures.

### 10.9.1 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 patient having to be withdrawn from the study which could potentially render that patient nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor.

### 10.9.2 Study Site Training and Ongoing Monitoring

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 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.

### 10.9.3 Quality Assurance Audits

An audit visit to clinical centers may be conducted by an 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.

### 10.9.4 Direct Access to Source Data/Documents for Audits and Inspections

Each investigator site is to maintain a record of locations of essential documents and study source documents. Members of the sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA, European Medicines Agency, or other regulatory agencies, as well as IRB representatives may also conduct an inspection of the study. If informed of such an inspection, the investigator should notify the sponsor immediately. 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 are available, if requested.

## 10.10 Clinical Study Report

A CSR will be prepared and provided to regulatory agency(ies), regardless of whether the study is completed, 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 CSR will be provided to the regulatory agency(ies) as required by the applicable regulatory requirements.

## 10.11 Publication and Disclosure Policy

The investigator agrees that all information received from the sponsor or designee, including, but not limited to, the IB, this protocol, eCRFs, the protocol-specified treatment, and any other study information, 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 prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure of this information 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 these 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]).[40] 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.

## 10.12 Investigator Oversight

The investigator has a responsibility for supervising any individual or party to whom they delegate study-related duties and functions conducted at the study site. This includes the services of any party or individual retained by the investigator for this purpose. All staff delegated study responsibilities must be documented on a 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-related duties, functions performed, and any data generated.

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# 12 APPENDICES

## Appendix 1 Modified Response Evaluation Criteria In Solid Tumors v1.1 and Prostate Cancer Working Group 3 Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer et al. 2009[41] and at http://www.eortc.be/Recist/Default.htm. and PCWG3 criteria as described by Scher, et al. 2016[42]

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 [LD] 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 (LD < 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 according to mRECIST criteria.

**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. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the 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.

**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.

**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 $\leq$ 5 mm contiguous reconstruction algorithm. If a site can document that the CT performed as part of a positron emission tomography (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, 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 and normalization of tumor marker level. |
| Stable Disease/Incomplete Response | Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits. |
| 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. |

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

**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 Non-Target 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

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[42]

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 study.

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, PET 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-methylene diphosphonate 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

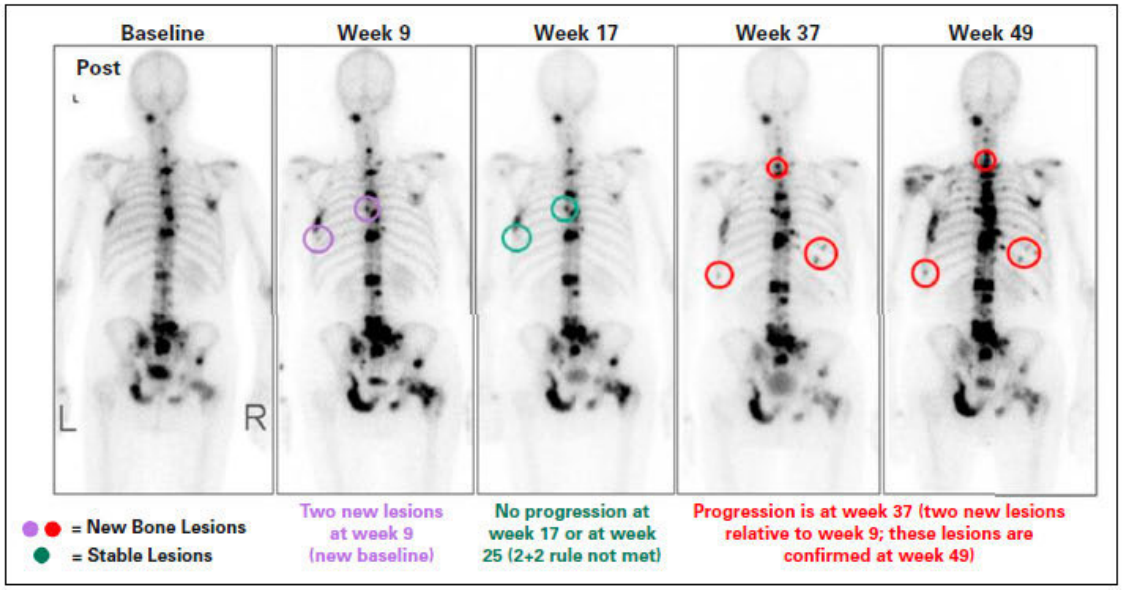
Documentation of baseline bone disease

- 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 first post-treatment scan, with at least two additional lesions on the next scan (2 + 2 rule)
- If at least two additional new lesions are seen on the next (confirmatory) scan, 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 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

## Appendix 1, Figure A: 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 mRECIST v1.1 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 compared to Week 9 on bone scan obtained at least 6 weeks after progression identified (or at Week 17 assessment) |
| Week 17 (2nd on-treatment scan) | Two or more new lesions on bone scan compared to **Week 9** bone scan. | Persistent or increase in number of bone lesions compared to Week 17 assessment on bone scan obtained at least 6 weeks after progression identified (or at Week 25 assessment) |
| Week 25 and after (3rd on-treatment scan and after) | Two or more new lesions bone scan compared to **Week 9** bone scan | Persistent or increase in number of bone lesions compared to prior assessment on bone scan obtained at least 6 weeks after progression identified (or at next scheduled assessment) |

# Appendix 2 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

| | |
|---|---|
| 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 3 Example Sensitive Clinical CYP Substrates (not an inclusive list)

| Examples of Sensitive Clinical CYP Substrate Drugs[a] | |
|---|---|
| **Enzyme or Transporter** | **Sensitive Substrate Drugs** |
| CYP1A2 | Tizanidine, theophylline, alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon |
| CYP2C9 | Celecoxib |
| CYP2C19 | S-mephenytoin, omeprazole |
| CYP3A | Alfentanil, sirolimus, tacrolimus, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan |

Source: FDA Guidance on Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-mediated Drug Interactions, January 2020.[43]

[a] This table is prepared to provide examples of clinical sensitive or moderate sensitive index substrates and is not intended to be an exhaustive list.

# Appendix 4 Example Inhibitors and Inducers of CYP2C8 and CYP3A4 (not an inclusive list)

| CYP Enzyme | Strong Inhibitor (Prohibited) | Moderate Inhibitor (Use with Caution) |
|---|---|---|
| CYP2C8 | clopidogrel<br>gemfibrozil | deferasirox<br>teriflunomide |
| CYP3A | boceprevir<br>clarithromycin<br>cobicistat<br>conivaptan<br>danoprevir and ritonavir<br>diltiazem<br>grapefruit juice[a]<br>idelalisib<br>indinavir and ritonavir<br>itraconazole<br>ketoconazole<br>lopinavir and ritonavir<br>paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)<br>nefazodone<br>nelfinavir<br>posaconazole<br>ritonavir<br>saquinavir and ritonavir<br>telaprevir<br>tipranavir and ritonavir<br>troleandomycin<br>voriconazole | aprepitant<br>cimetidine<br>ciprofloxacin<br>clotrimazole<br>crizotinib<br>cyclosporine<br>dronedarone<br>erythromycin<br>fluconazole<br>erythromycin<br>imatinib<br>tofisopam<br>verapamil |
| **CYP Enzyme** | **Strong Inducer (Contraindicated)** | **Moderate Inducer (Contraindicated)** |
| CYP3A | carbamazepine<br>mitotane<br>phenytoin<br>rifampin<br>St. John's Wort | bosentan<br>efavirenz<br>etravirine<br>modafinil |

Source: FDA Guidance on Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-mediated Drug Interactions, January 2020.[43]

[a] The effects of grapefruit juice vary widely among brands, thus can be classified as both a strong and moderate inhibitor depending on concentration, quantity consumed, and preparation. Patients should be advised to avoid.