Clinical Study Protocol: CO-338-085

Study Title:	ATLAS: A Phase 2, Open-label Study of Rucaparib in Patients with Locally Advanced or Metastatic Urothelial Carcinoma
Study Number:	CO-338-085
Study Phase:	Phase 2
Product Name:	Rucaparib (CO-338)
IND Number:	[redacted]
EUDRA CT Number:	[redacted]
Indication:	Locally advanced unresectable or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra)
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted]
Responsible Medical Officer:	[redacted]

	Date
[redacted]	[redacted]
Amendment 1:	24 October 2018

Confidentiality Statement

PROTOCOL APPROVAL SIGNATURE PAGE

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Version:	Amendment 1

PROTOCOL ACCEPTANCE FORM

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Date:	24 October 2018
Version:	Amendment 1

I have carefully read this protocol and agree that it contains all 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:

Clinical Investigators, Study Sites, and Laboratories:

SYNOPSIS

Sponsor Clovis Oncology, Inc.
Name of Finished Product Rucaparib tablets
Name of Active Ingredient Rucaparib camsylate (CO-338)
Study Title ATLAS: A Phase 2, Open-label Study of Rucaparib in Patients with Locally Advanced or Metastatic Urothelial Carcinoma
Study Number CO-338-085
Study Phase Phase 2
Rationale Bladder cancer is the ninth most common cancer worldwide and amongst the 6 most common cancers in the United States (US) and Europe.[1,2] In the US, it is estimated that there will be over 79,000 new cases of bladder cancer and over 16,000 deaths from bladder cancer in 2017.[1] Muscle invasive bladder cancer (MIBC) is a platinum-sensitive disease with cisplatin-containing chemotherapy being the preferred first-line treatment in the adjuvant setting.[3] Although the initial response rate for cisplatin-containing chemotherapy ranges from 49% to 72%, most patients will have disease relapse within 9 months.[4,5] For patients ineligible to receive cisplatin, treatment with carboplatin-containing chemotherapy or an immune checkpoint inhibitor is typically administered in the first-line setting; however, the response rate and time to progression are less than cisplatin-containing chemotherapy.[3] After disease relapse, the choice of treatment in the second-line setting includes immune checkpoint inhibitors, single-agent docetaxel, single-agent paclitaxel, and single-agent vinflunine. A majority of patients will have progression of their disease within 2 to 3 months of starting treatment for relapsed disease.[6] Options are limited after treatment with platinum-containing chemotherapy and/or an immune checkpoint inhibitor, therefore additional therapies are needed. Inhibition of deoxyribonucleic acid (DNA) damage repair in cancer cells represents an attractive opportunity for the development of new therapies. In normal cells, single-strand breaks (SSBs) in DNA are repaired through base excision repair (BER) via poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination repair (HRR) of DNA, a complex process involving multiple proteins. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect on cancer cell death. However, inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. For example, normal cells treated with a PARP inhibitor still have other intact DNA repair pathways that are able to survive, whereas cancer cells with pre-existing homologous recombination deficiency (HRD) that are treated with a PARP

inhibitor accumulate DNA damage and enter apoptosis. This concept of synthetic lethality has been demonstrated in key in vitro and in vivo studies, as well as in several clinical studies that evaluated a single-agent PARP inhibitor.[7-9]

Homologous recombination pathway defects, either as an initiating event or a late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. Targeted next-generation sequencing (NGS) of bladder cancer tumor DNA has shown that approximately 11% of tumors have HRD resulting from mutations in DNA repair pathway genes.[10] HRD has been demonstrated to predict response to cisplatin-based chemotherapy in bladder cancer patients.[10,11] In addition to deleterious mono- or bi- allelic alterations in HRR genes, tumors often have other genomic and/or epigenetic deficits that can drive HRD and cause distinct genomic signatures. For example, genome-wide loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and chromosomal breaks are all phenotypic markers of HRD.[12] Based on an analysis of The Cancer Genome Atlas (TCGA) bladder cancer data set (http://cancergenome.nih.gov), approximately 60% of bladder cancer tumors may have HRD (Clovis, data on file). In the same data set, platinum-chemotherapy treated bladder cancer patients with tumors that demonstrated evidence of HRD had improved survival as compared to bladder cancer patients with tumors without evidence of HRD (Clovis, data on file).

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3, that has demonstrated preclinical and clinical activity in cancers associated with a deleterious mutation in breast cancer gene 1 and 2 (BRCA1/2)[1] or other HRR gene, and/or high level of genomic LOH. Rucaparib was approved in December 2016 by the US Food and Drug Administration (FDA), followed by regular approval in April 2018, for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced epithelial ovarian cancer (EOC), fallopian tube (FTC), or primary peritoneal cancer (PPC) who have been treated with 2 or more chemotherapies.[13,14] In May 2018, the European Commission authorized rucaparib (Rubraca) 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.[15] In April 2018, rucaparib was approved in the US by the FDA for maintenance treatment for adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[14] In the study supporting this approval, rucaparib demonstrated improved progression-free survival (PFS) as maintenance treatment following response to platinum-based chemotherapy. Although tumor HRD status was predictive of response to rucaparib, activity was also observed in patients with HRD-negative tumors, suggesting an incomplete understanding of the biomarkers responsible for PARP inhibitor sensitivity in ovarian cancer.[16]

The purpose of this study is to evaluate the efficacy and safety of monotherapy rucaparib as treatment for patients with locally advanced unresectable or metastatic urothelial bladder cancer. The study will enroll approximately 200 patients, regardless of HRD

[1] The typical convention is to use italicized names for genes and plain text names for proteins. However, in this document, BRCA mutations which occur at both the gene and protein level are often discussed. Therefore, for enhanced readability, BRCA and other genes are written in plain text only throughout this document.

status, who have received 1 or 2 prior treatment regimens. Enrollment of patients, regardless of HRD status, who have received ≤ 2 prior treatments, is appropriate given that available treatment options are limited and both HRD-positive and HRD-negative patients may potentially respond to treatment with rucaparib. Primary efficacy will be assessed in a prospectively defined HRD-positive population as well as the intent-to-treat (ITT) population. Additional secondary and exploratory efficacy and safety endpoints will also be evaluated in HRD subgroups and the ITT population.

Primary Objective:

- To evaluate objective response rate (ORR) in molecularly-defined homologous recombination deficiency (HRD)-positive and intent-to-treat (ITT) populations using a prospectively defined molecular signature.

Secondary Objectives:

- To evaluate duration of response (DOR)
- To estimate progression-free survival (PFS)
- To estimate overall survival (OS)
- To evaluate the safety and tolerability of rucaparib
- To evaluate steady-state pharmacokinetics (PK) of rucaparib

Exploratory Objectives:

- To assess biomarkers that correlate with response to rucaparib
- To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to rucaparib
- To assess molecular changes over time in plasma and tumor samples
- To evaluate biomarkers associated with resistance to rucaparib

Study Design

This is a Phase 2 multicenter, open-label study evaluating rucaparib for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma. This study will enroll patients with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1). All patients must have received 1 or 2 prior treatment regimens and have radiologic progression during or after the most recent regimen. Patients who have received prior PARP inhibitor treatment will be excluded. Tumor tissue will be analyzed to determine HRD status (HRD-positive or HRD-negative) prior to efficacy analyses.

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

Screening Phase

Each patient, with the following exceptions, will undergo a biopsy for collection of tumor tissue. Tumor tissue samples should be from primary or metastatic soft tissue tumor (see Section 7.6.5.1 for details). Patients who had tumor tissue collected as part of standard of care ≤ 6 months prior to the first planned dose of rucaparib and had no intervening anti-cancer treatments during this period are not required to have a biopsy at screening, provided that adequate tumor tissue can be provided for analysis. An archival tumor

sample, if available, must also be submitted in addition to the mandatory collection of tumor tissue (See Section 7.6.5.2).

Additional screening assessments will include demographics and medical history, prior anti-cancer treatments, prior and current medications and procedures, 12-lead electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status, local laboratory hematology and serum chemistry measurements, serum pregnancy test (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, adverse events (AEs), and tumor assessment by computed tomography (CT) scan.

Patients must meet all inclusion and exclusion criteria as specified in the protocol.

Treatment Phase

Patients will be administered rucaparib at a starting dose of 600 mg orally twice daily (BID) for continuous 28-day cycles and will undergo procedures and assessments including regular safety, PK, and efficacy evaluations during the entire conduct of the study. Biomarker blood samples will be collected for ctDNA and genomic DNA analysis (see Section 7.6.6 and 7.6.7, respectively). Tumor assessments by CT scan will be performed every 8 calendar weeks (±7 days) from Cycle 1 Day 1 up to 18 months and then every 12 calendar weeks (±7 days) thereafter and at the End of Treatment Visit, if applicable. Copies of tumor scans (and other imaging, as appropriate) will be collected from all patients in the study. Patients will continue on rucaparib until radiologic progression per RECIST v1.1 as assessed by the investigator, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, withdrawal of consent, or patient is lost to follow-up. If a patient has radiologic progression per RECIST v1.1, but is deriving clinical benefit in the opinion of the investigator, then continuation of treatment beyond progression is permitted. In such cases, the decision to continue must be documented in source documents and the patient must provide additional consent prior to continuing treatment with rucaparib.

Safety and efficacy data will be periodically reviewed by the Data Monitoring Committee (DMC).

Post-treatment Phase

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

If treatment was discontinued for reasons other than radiologic disease progression or death, radiologic tumor assessment (using the same methodology as was used at initial study screening) will continue until confirmed radiographic disease progression by RECIST v1.1 per investigator, death, loss to follow-up, withdrawal from the study, study closure, or initiation of subsequent treatment. Ongoing serious adverse events (SAEs), adverse events of special interest (AESIs), and treatment-related Grade 3/4 AEs will be followed until either resolution or stabilization has been determined or until patient is lost to follow-up. After the 28-day Follow-up Visit, only related SAEs and all AESIs, irrespective of causality, need to be reported.

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

Number of Patients

Approximately 200 patients will be enrolled.

Number of Sites

Patients will be enrolled at approximately 65 sites worldwide.

Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the Informed Consent Form (ICF) is signed.
3. Have histologically or cytologically confirmed locally advanced unresectable (tumor, node, metastasis [TNM] staging of T4b and any N; or any T and N2-3) or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureter, urinary bladder, or urethra). Mixed transitional/non-transitional cell histologies are allowed.
4. Received 1 or 2 prior treatment regimens (eg, cisplatin- or carboplatin-containing chemotherapy, immune checkpoint inhibitor, and/or clinical trial) for locally advanced unresectable or metastatic disease and had confirmed radiologic disease progression during or following the most recent treatment. The principal investigator is responsible for ensuring the patient has received anti-cancer treatment as appropriate in the country of enrollment, taking into account the patient's current health status as well as how the patient responded to/tolerated prior treatment(s).
    a. Neoadjuvant and/or adjuvant treatment for muscle invasive disease will be considered a treatment regimen if radiologic disease progression occurred ≤ 12 months from the completion of treatment.
    b. No more than 1 prior platinum-containing chemotherapy regimen for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.
    c. For patients who have never received platinum, the patient must currently be ineligible for or refuse cisplatin treatment.
    d. A treatment regimen that is held for reasons other than progression which is subsequently resumed at a later date with no other intervening systemic anti-cancer treatment is considered 1 treatment regimen.
5. Mandatory tumor tissue must be collected ≤ 28 days prior to the first dose of rucaparib treatment. A biopsy or surgical resection of tumor tissue is required, unless archival tumor tissue collected ≤ 6 months prior to the first dose of rucaparib is available and no intervening anti-cancer treatments were administered

during this period. Tumor tissue should be of adequate quality for molecular profiling. (See Section 7.6.5.1)

6. Have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1). A measurable tumor lesion in a previously irradiated site is acceptable if subsequent progression has been demonstrated in that lesion.
7. Have adequate organ function confirmed by the following laboratory values obtained ≤ 14 days prior to first dose of rucaparib:
    a. Bone Marrow Function
        i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
        ii. Platelets > 100×10^9/L
        iii. Hemoglobin ≥ 9 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
    c. Renal Function
        i. Measured or calculated creatinine clearance (CrCL) ≥ 30 mL/min or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. For calculated CrCL or eGFR, the Cockcroft Gault formula or institutional standard formula can be used.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 14 days prior to first dose of rucaparib.
9. Have life expectancy ≥ 12 weeks.

Exclusion Criteria

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

1. Active second malignancy for which patient has received treatment within 2 years prior to the first dose of rucaparib with exception for the following circumstances:
    a. Curatively treated non-melanoma skin cancer.
    b. Non-invasive diseases such as low risk cervical cancer or any cancer in situ.
    c. Localized (early stage) cancer treated with curative intent (without evidence of recurrence and intent for further therapy) and in which no systemic therapy was indicated.
2. Prior treatment with a PARP inhibitor.
3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks prior to the first dose of rucaparib.

4. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib.
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C.
6. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib (See Section 4.4).
    b. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to the first dose of rucaparib. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
    c. Male patients who refuse to use condoms during sex. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib.
7. Received anti-cancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of rucaparib and/or ongoing treatment-related adverse events National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) > Grade 1 except for neuropathy, ototoxicity, alopecia, and electrolyte abnormalities.
8. Non-study 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.
9. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

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

Study Treatment

Patients will take 600 mg rucaparib orally BID, as close to 12 hours apart as possible and preferably at the same times every day, with water starting on Day 1. Rucaparib tablets must be swallowed whole and may be taken with or without food. Rucaparib may 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 reductions and dose holds are permitted in the event of unacceptable toxicity.

Concomitant Medications

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

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

Palliative radiotherapy for the treatment of lesions not considered target lesions for tumor assessments is permitted during the study.

No other anti-cancer therapies (including chemotherapy, radiation, antibody, immunotherapy, gene therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is receiving rucaparib.

Caution should be used for concomitant medications that are sensitive clinical substrates of cytochrome P450 (CYP) 1A2, CYP2C9, CYP2C19, and/or CYP3A.

Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

Caution is advised when metformin or a medicine that is a breast cancer resistance protein (BCRP) substrate (eg, rosuvastatin) is co-administered with rucaparib.

Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 *in vivo* cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

Treatment Discontinuation Criteria

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

a. 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);
b. Progression per RECIST v1.1 of patient's underlying cancer (unless, in the opinion of the investigator, the patient continues to derive clinical benefit);
c. Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
d. An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy;
e. Noncompliance by the patient with protocol mandated procedures; and/or
f. A positive pregnancy test at any time during the study.

Efficacy Assessments

Efficacy measures will include tumor assessments using CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1 and clinical examination; other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET]/CT, bone scan, and ultrasound) may be performed as clinically indicated. MRI may be used in place of CT scans for assessment of target lesions if required by local authorities. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous [IV] and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. Disease assessments will be performed during screening, at the end of every 8 calendar weeks (±7 days) during the treatment and post-treatment (if patient discontinued treatment for any

reason other than radiologically confirmed disease progression or death) phases until radiologically confirmed disease progression, withdrawal of consent, loss to follow-up, death, initiation of subsequent treatment, or study closure. Disease assessments should also be done at the end of treatment if it has been ≥ 8 calendar weeks since the last assessment. Patients who have been on study at least 18 months may decrease the frequency of tumor assessments to every 12 calendar weeks (±7 days). If a complete response (CR) or partial response (PR) is noted, confirmatory scans should be performed at least 4 weeks after response was first documented.

Copies of tumor scans (and other imaging, as appropriate) will be collected from all patients in the study. Independent radiology review (IRR) may be conducted on all or a subset of tumor scans collected.

Safety Assessments

Safety and tolerability will be assessed based on the following:

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

Statistical Methods

Sample Size

The overall sample size was determined by considering the number of patients needed for adequate safety and activity assessment of HRD-positive patients. Based on the estimated prevalence of 60% HRD-positive patients in this population, approximately 200 patients will be enrolled into the study. This would result in enrollment of approximately 120 HRD-positive patients.

Efficacy Analysis

Response will be determined using RECIST v1.1. The ORR will be summarized with frequencies and percentages. The DOR will be summarized with descriptive statistics (N, mean, standard deviation [StD], median, minimum, and maximum) as well as categorically. Kaplan-Meier methodology will be used to summarize time to event variables. The efficacy analyses will be evaluated for the HRD-positive subgroup, the ITT population, and other HRD subgroups.

Safety Analyses

Adverse events, clinical laboratory results, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. Adverse events will be summarized overall and separately for SAEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE (Version 4.03 or later) Grade 3 or higher AEs. Body weight and vital signs will be summarized descriptively (N, mean, StD, median, minimum, and maximum). ECOG performance status will be summarized categorically.

Data Monitoring Committee

The study will have a formal Data Monitoring Committee (DMC) that will include coordinating investigators and sponsor personnel. The DMC will review both safety and efficacy data.

Interim Safety Monitoring

A formal safety data review will occur after the first 20 patients have been enrolled and completed the first cycle of treatment, and then approximately every 6 months thereafter. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

Interim Efficacy Analysis

A group sequential interim monitoring plan will be implemented in order to help guide the DMC in monitoring the study. The null hypothesis is p=0.10 based on historical data in similar patient populations. The study has greater than 90% power to reject the null hypothesis at a 5% significance level if the true response rate for rucaparib is 20%.

Interim analyses will be performed when approximately 60 patients and 120 patients have complete data, defined as a documented response (PR or CR), disease progression, or at least 4 months of disease assessment data available.

Additional details regarding this interim monitoring plan are provided in Appendix 4.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADP	adenosine diphosphate
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice daily
BRCA	breast cancer gene
BRCA1/2	breast cancer gene 1 or breast cancer gene 2
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLIA	Clinical Laboratory Improvement Amendment
C_{max}	maximum plasma concentration
C_{min}	trough plasma concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CrCL	creatinine clearance
CRF	Case Report Form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
CV	coefficient of variation
CYP	cytochrome P450
ddMVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DDI	drug-drug interaction(s)

DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSB(s)	double-strand break(s)
ECG(s)	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOT	End of Treatment
F	bioavailability
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FTC	fallopian tube cancer
gBRCA	germline mutation in BRCA
GC	gemcitabine and cisplatin
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HDPE	high-density polyethylene
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HRD	homologous recombination deficient or homologous recombination deficiency
HRR	homologous recombination repair
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF(s)	Informed Consent Form(s)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Inc.	Incorporated
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IRR	independent radiology review
ITT	intent-to-treat
IUD	intrauterine device

IUS	intrauterine system
IV	intravenous
IWRS	Interactive Web Response System
LD	longest diameter
LDH	lactate dehydrogenase
LOH	loss of heterozygosity
LST	large-scale state transitions
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
MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NGS	next-generation sequencing
NMIBC	non-muscle-invasive bladder cancer
NYHA	New York Heart Association
OCT	organic cation transporter
ORR(s)	objective response rate(s)
OS	overall survival
PALB2	partner and localizer of BRCA2
PARP	poly(ADP-ribose) polymerase
PPC	primary peritoneal cancer
PD	progressive disease (in context of disease monitoring)
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI(s)	proton pump inhibitor(s)
PR	partial response or PR interval
PT	Preferred Term
QD	once daily
QRS	QRS complex/interval
QT	QT interval
RAD51C	RAD51 paralog C

RAD51D	RAD51 paralog D
RBC(s)	red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease (in context of disease monitoring)
SI	International System of Units
SOC	System Organ Class
SOP(s)	standard operating procedure(s)
SSB(s)	single-strand break(s)
StD	standard deviation
SUSAR(s)	suspected unexpected serious adverse reaction(s)
$T_{1/2}$	terminal half-life
TA1	telomeric-allelic imbalance
tBRCA	tumor tissue mutation in BRCA1/2, includes germline BRCA and somatic BRCA
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
T_{max}	time of occurrence of C_{max}
TNM	tumor, node, metastasis
UDP	uridine diphosphate
UGT	uridine diphosphate-glucuronosyl transferase
ULN	upper limit of normal
US	United States
WBC(s)	white blood cell(s)
WHO	World Health Organization

1 INTRODUCTION

1.1 Urothelial Carcinoma

1.1.1 General Overview

Bladder cancer is the ninth most common cancer worldwide and amongst the 6 most common cancers in United States (US) and Europe.[1,2] In the US, it is estimated there will be over 79,000 new cases of bladder cancer and over 16,000 deaths from bladder cancer in 2017.[1] Bladder cancer is more common in men than women (ratio 3:1), and the median age at diagnosis is approximately 70 years.[17] Urothelial (transitional cell) carcinoma, which develops in the renal pelvis, ureter, urinary bladder, and/or proximal two-thirds of the urethra, accounts for approximately 90% of bladder cancers. Tumors are staged using the tumor, node, metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC) and classified as non-muscle-invasive bladder cancer (NMIBC)(tumors $\leq$ stage T1) or muscle-invasive bladder cancer (MIBC)(tumors $\geq$ stage T2).[18] Treatment recommendations are divided according to NMIBC and MIBC.

NMIBC, low grade tumors ($\leq$ stage T1) that have not invaded the muscle, accounts for approximately 70% of newly diagnosed bladder cancer. With current treatments, the 5-year relative survival is over 95% for in situ disease and 70% for stage T1.[1] Despite these survival rates, 50% to 70% of NMIBC will recur with 10% to 15% of patients progressing to MIBC.[17]

MIBC, tumors $\geq$ stage T2 that have invaded the muscle, accounts for approximately 30% of newly diagnosed bladder cancer. Unlike NMIBC, prognosis for MIBC is poor with a 5-year survival rate of 35% for stage T2 and 5% for patients with distant metastases.[1] Overall survival (OS) after initial therapy is 15 months or shorter in this population.[4,5]

1.1.2 Treatment of Muscle-invasive Urothelial Carcinoma

The initial treatment course for MIBC includes neoadjuvant cisplatin-containing chemotherapy, surgery (ie, radical cystectomy, partial cystectomy, or bladder preserving procedures), radiation, and/or adjuvant chemotherapy. MIBC is a platinum-sensitive disease with cisplatin-containing chemotherapy being the preferred first-line treatment in the adjuvant setting.[3] The 2 commonly used regimens are a combination of gemcitabine and cisplatin (GC) and a combination of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC). The median OS in patients with metastatic disease for GC and ddMVAC is 13 to 15 months.[4,5] Although the initial response rate for cisplatin-containing chemotherapy ranges from 49% to 72%, most patients will have disease relapse within 9 months.[4,5] For patients who are cisplatin ineligible (patients meeting at least 1 of the following: World Health Organization [WHO] or Eastern Cooperative Oncology Group [ECOG] performance status > 2, or Karnofsky performance status of 60% to 70%, creatinine clearance [CrCL; calculated or measured] < 1 mL/s, > National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Grade 2 audiometric hearing loss, > CTCAE Grade 2 peripheral neuropathy, or New York Heart Association [NYHA] class III heart failure),[19] a combination of carboplatin and gemcitabine can be administered. Until recently, the standard of care for patients who progressed after first-line treatment

included single-agent docetaxel, single-agent paclitaxel, single-agent vinflunine, and treatment in clinical studies The median OS for these second-line therapies is approximately 6 to 9 months with objective response rates (ORRs) of 10% to 20%.[6]

Recently, immune checkpoint inhibitors have rapidly changed the standard of care for treatment of urothelial carcinoma in the second-line setting, as well as in the first-line setting for patients ineligible for cisplatin-containing chemotherapy. Several immune checkpoint inhibitors, including atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab, have received either full or accelerated approval by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) in the second-line setting following progression on a platinum-based treatment. The median OS observed with these therapies ranges from 7 to 18 months, with ORRs ranging from 15% to 21% regardless of programmed death ligand 1 (PD-L1) expression.[20-24] Based on these data, immune checkpoint inhibitors are now included in guidelines for second-line treatment of metastatic bladder cancer following first-line platinum-based therapy and are rapidly becoming standard of care treatment in the US.[18]

For patients who are not eligible to receive cisplatin in the first-line setting, atezolizumab and pembrolizumab are FDA approved agents in this setting. The ORR for atezolizumab and pembrolizumab is 23% and 29%, respectively.[25,26] Use of these immune checkpoint inhibitors in this treatment setting is increasing and they are rapidly becoming standard of care treatment.[18]

Despite recent advancements in treatment, many patients do not respond to treatment and subsequently have rapid disease progression. Therefore, additional therapy options are warranted in this patient population.

1.2 Mechanism of PARP Inhibition and Homologous Recombination Deficiency

Deoxyribonucleic acid (DNA) is constantly damaged by both endogenous and exogenous (environmental) assaults which can result in the formation of single-strand breaks (SSBs). Normal cells repair SSBs in DNA through a process known as base excision repair (BER).[27] While there are several pathways for BER, all pathways rely on the activity of poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) enzymes. In humans, the PARP family encompasses 17 enzymes, of which PARP-1 is the best characterized.[28] SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are, in turn, repaired by homologous recombination repair (HRR), a complex process involving multiple proteins, including the breast cancer genes 1 and 2 (BRCA1[2] and BRCA2).[27]

[2] The typical convention is to use italicized names for genes and plain text names for proteins. However, in this document, BRCA mutations which occur at both the gene and protein level are often discussed. Therefore, for enhanced readability, BRCA and other genes are written in plain text only throughout this document.

PARP inhibitors have shown activity in BRCA1 and BRCA2 (BRCA1/2) mutant and homologous recombination deficient (HRD) cancers through a mechanism known as synthetic lethality, in which the loss of 2 DNA repair pathways is required for cell death. For example, the inhibition of BER from PARP inhibition in a tumor cell with an underlying defect in HRR (eg, BRCA1/2 mutation) results in tumor cell death through the accumulation of unrepaired DNA damage. Alternatively, homologous recombination proficient cells are able to repair SSBs resulting from PARP inhibition.[7,8,27]

Multiple genomic and epigenetic alterations can render tumor cells HRD and sensitive to PARP inhibition. For example, PARP inhibitors have demonstrated activity in tumor cells with deleterious mutations in genes of the HRR pathway such as BRCA1/2, RAD51 paralog C (RAD51C), RAD51 paralog D (RAD51D), and partner and localizer of BRCA2 (PALB2). Epigenetic modifications such as BRCA1 and RAD51C promoter hypermethylation have also been shown to result in HRD and confer sensitivity to PARP inhibitors. Given that multiple genetic and epigenetic mechanisms can render a tumor cell HRD, phenotypic genomic biomarkers have been explored to identify these cells. For example, genomic loss of heterozygosity (LOH) results from the accumulation of DNA damage in HRD tumors through the use of error-prone DNA repair pathways.[29,30] Tumors with extensive genome-wide LOH, or loss of large chromosomal regions, have been shown to be sensitive to PARP inhibition.[16,31] Another genomic signature that has been shown to identify patients who are more sensitive to PARP inhibition is a biomarker HRD score which combines 3 independent measures of HRD (LOH, telomeric-allelic imbalance [TAI], and large-scale state transitions [LST]). This combination signature has been shown to confer increased sensitivity to PARP inhibition in tumors with a high HRD score when compared to tumors with a low HRD score.[32] Notably, these genomic signatures can readily be assessed in tumors by next-generation sequencing (NGS).[29,30] One of the main advantages of assessing HRD using genomic signatures is their ability to identify HRD tumors regardless of the underlying mechanisms due to the phenotypic nature of the signature.[33,34]

In ovarian cancer, it is estimated that half of all high-grade serous tumors have HRD, with approximately 15% of carcinomas harboring a germline BRCA mutation, 6% a somatic BRCA mutation, and 20% a mutation in, or epigenetic silencing of, another HRR gene. Even without an identifiable BRCA or other known HRR gene mutation, many high-grade serous ovarian carcinomas display BRCA-like genomic signatures. Rucaparib has been evaluated as both a treatment and maintenance therapy for women with ovarian cancer. The results from the randomized Phase 3 Study CO-338-014 (ARIEL3; NCT01968213), which assessed progression-free survival (PFS) with rucaparib as a maintenance therapy following platinum-based chemotherapy for patients with platinum-sensitive, recurrent ovarian carcinoma, have been published.[16] The PFS was significantly longer in the BRCA-mutant and BRCA wild-type/LOH high groups compared to the BRCA wild-type/LOH low group; however, platinum-sensitive patients treated with rucaparib demonstrated a significant benefit compared to placebo in PFS regardless of mutation status (BRCA-mutant, LOH high, and intent-to-treat [ITT] populations). Although HRD was predictive of response to rucaparib, activity was also observed in the ITT population, suggesting an incomplete understanding of the biomarkers responsible for PARP inhibitor sensitivity in ovarian cancer.[16]

While BRCA1/2 mutations are less prevalent in bladder cancer, targeted NGS of bladder cancer tumors has shown that approximately 11% of tumors have HRD resulting from mutations in DNA repair pathway genes.[10] HRD has been demonstrated to predict response to cisplatin-based chemotherapy: patients with tumors that demonstrated evidence of HRD have been shown to benefit more from platinum chemotherapy than patients with tumors without evidence of HRD.[10,11] In addition to deleterious mono- or bi- allelic alterations in HRR genes, tumors often have other genomic and/or epigenetic deficits that can drive HRD and cause distinct genomic signatures. For example, genome-wide LOH, telomeric allelic imbalance (TAI), and chromosomal breaks are all phenotypic markers of HRD that are prevalent in bladder cancer tumors. Analysis of The Cancer Genome Atlas (TCGA) bladder cancer data set (http://cancergenome.nih.gov) indicates that approximately 10% of bladder cancer tumors harbor a deleterious alteration in an HRR gene (Clovis, data on file). Additionally, genomic scars were detected in tumor samples without any HRR gene alterations, suggesting that, overall, approximately 60% of bladder cancer tumors may have HRD without having an alteration in a gene of the HRR pathway (Clovis, data on file). In the same data set, platinum-chemotherapy treated patients with above-median levels of HRD had improved survival when compared to patients with below-median levels of HRD: for these HRD subgroups the OS hazard ratio was 0.45 and statistically significant (Wald-p=0.03)(Clovis, data on file).

Given the prevalence of alterations in genes of the HRR pathway and the high incidence of non-mutation mediated HRD, it is reasonable to estimate that approximately 60% of all bladder cancer patients may exhibit HRD.

1.3 Rucaparib

1.3.1 Background

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3 that has demonstrated preclinical and clinical activity in cancers associated with a deleterious mutation in BRCA1/2 or other HRR gene and/or high level of genomic LOH. Rucaparib was approved by the US FDA in December 2016 for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with 2 or more chemotherapies.[13,14] In May 2018, the European Commission authorized rucaparib (Rubraca) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.[15] More recently, rucaparib demonstrated improved PFS in the maintenance treatment of patients with recurrent platinum-sensitive ovarian cancer. Although HRD was predictive of response to rucaparib, activity was also observed in HRD-negative patients, suggesting an incomplete understanding of the biomarkers responsible for PARP inhibitor sensitivity.[16]

Clovis Oncology, Inc. (Clovis; sponsor) is developing rucaparib for oral administration in patients with evidence of HRD, including locally advanced unresectable or metastatic

transitional cell carcinoma of the urothelium including renal pelvis, ureter, urinary bladder, and urethra.

1.3.2 Prior Experience with Rucaparib

An overview of data from nonclinical and clinical studies of rucaparib are provided below and described in detail in the rucaparib Investigator's Brochure (IB). A summary of the benefit: risk is also provided in the rucaparib IB.

1.3.2.1 Nonclinical Experience with Rucaparib

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

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

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistance 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 after oral dosing.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 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.[35-38]

1.3.2.2 Clinical Experience with Rucaparib

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer who have evidence of HRD. There are 4 clinical studies in patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer: a Phase 2 study in patients whose cancer is associated with a germline BRCA (gBRCA) mutation (Study CO-338-010 [Study 10]); a Phase 2 biomarker study (Study CO-338-017 [ARIEL2]) designed to refine the molecular signature based on HRD associated with a response to rucaparib; a randomized, placebo-controlled Phase 3 study (Study CO-338-014 [ARIEL3]) evaluating rucaparib as switch maintenance treatment; and Phase 3 Study CO-338-043 (ARIEL4), which is evaluating rucaparib versus chemotherapy in BRCA1/2-mutant ovarian cancer patients with relapsed disease.

Phase 2 Study CO-338-052 (TRITON2) and Phase 3 Study CO-338-063 (TRITON3) are evaluating rucaparib as treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) associated with HRD. An additional Phase 2 study in mCRPC patients is evaluating rucaparib in combination with nivolumab.

Additional studies of rucaparib as monotherapy and in combination with other anti-cancer therapies in ovarian, prostate, and urothelial cancer, as well as other tumor types, are ongoing or planned.

The rucaparib clinical studies and results are described in more detail in the rucaparib IB.

1.3.2.2.1 OVERVIEW OF CLINICAL PHARMACOLOGY

Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or twice daily (BID) dosing, rapid absorption with maximum plasma concentration (C_{max}) achieved within 1.5 to 6 hours. The oral bioavailability was 36% and terminal 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. At the target clinical dose of 600 mg, a high-fat meal increased the C_{max} and area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) of rucaparib by 20% and 38%, respectively, and delayed the median time to occurrence of C_{max} (T_{max}) by approximately 2.5 hours as compared with these parameters 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 analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and

hyperinducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play a limited role in rucaparib metabolism in vivo. 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 drug-drug interactions (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.

1.3.2.2.2 OVERVIEW OF EFFICACY

1.3.2.2.2.1 Ovarian Cancer Treatment Indication

On 19 December 2016, the FDA granted accelerated approval, followed by regular approval in April 2018, for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated EOC, FTC, or PPC who have been treated with ≥ 2 chemotherapies.[14] In May 2018 , the European Commission authorized rucaparib (Rubraca) 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.[15] The recommended dose of rucaparib is 600 mg BID.

The basis for the approval of rucaparib as monotherapy for the treatment of ovarian cancer are the data sets and analyses for patients with advanced ovarian cancer comprising the primary efficacy analysis population. The primary efficacy analysis population included 106 patients, of whom 79 were platinum-sensitive, pooled from the open-label, single-arm Phase 2 studies, Study CO-338-010 Part 2A and Study CO-338-017 Parts 1 and 2, with BRCA-mutant ovarian cancer, who had received ≥ 2 prior chemotherapy regimens, at least 2 of which were platinum-based, and who had received at least 1 dose of 600 mg rucaparib.[14]

The primary endpoint on which approval was based is investigator-assessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1), with ORR by central independent radiology review (IRR) conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR by IRR was 41.5%, confirming the results of investigator assessment for this endpoint.[13] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.[13]

1.3.2.2.2.2 Ovarian Cancer Maintenance Indication

In April 2018, rucaparib (Rubraca) was approved in the US by the FDA for maintenance treatment for adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[14] Efficacy of rucaparib monotherapy for patients with advanced ovarian cancer in the maintenance setting was demonstrated from Study CO-338-014 results showing significant benefit of rucaparib compared to placebo across primary, secondary, and exploratory endpoints.[16] In this study, investigator-assessed PFS was the primary efficacy endpoint, with PFS by blinded central IRR conducted as a key, stand-alone, secondary endpoint. Rucaparib maintenance treatment significantly improved PFS compared with placebo in all primary analysis groups of patients with recurrent ovarian cancer after a complete or partial response to platinum-based therapy (Table 1). Overall, rucaparib as maintenance treatment reduced the risk of progression by 63.5% (hazard ratio 0.365 [95% CI, 0.295 0.451]; $p < 0.0001$) in the ITT population, demonstrating a strong treatment effect over placebo. Analysis of non-nested, non-overlapping patient subpopulations indicate that the significant improvement in PFS observed in the ITT population was not driven only by the HRD or tBRCA (tumor tissue mutation in BRCA) subpopulations (Table 1). Nearly half (44.6%) of the patients in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group.[16] At 18 and 24 months, 32.0% and 26.0%, respectively, of patients who received rucaparib were still progression-free compared to 5.8% and 2.6% in the placebo group.[16] These investigator-assessed results were confirmed by results of central IRR assessment (Table 1).[16]

Table 1. Progression-free Survival per Investigator and per IRR in Primary Analysis Populations in Study CO-338-014

Analysis Population	PFS by Investigator Review (Primary Endpoint)		PFS by Blinded, Central IRR (Key Secondary Endpoint)	
	Median PFS (months) Rucaparib vs Placebo[a]	Hazard Ratio[b]	Median PFS (months) Rucaparib vs Placebo[a]	Hazard Ratio[b]
Primary Analysis Groups				
tBRCA (rucaparib n = 130; placebo n = 66)	16.6 vs. 5.4 (p < 0.0001)	0.231 (p < 0.0001)	26.8 vs. 5.4 (p < 0.0001)	0.201 (p < 0.0001)
HRD (rucaparib n = 236; placebo n = 118)	13.6 vs. 5.4 (p < 0.0001)	0.317 (p < 0.0001)	22.9 vs. 5.5 (p < 0.0001)	0.336 (p < 0.0001)
ITT (rucaparib n = 375; placebo n = 189)	10.8 vs. 5.4 (p < 0.0001)	0.365 (p < 0.0001)	13.7 vs. 5.4 (p < 0.0001)	0.354 (p < 0.0001)
Exploratory Analysis of Non-nested Subgroups				
Non-tBRCA LOH+ (rucaparib n = 106; placebo n = 52)	9.7 vs. 5.4 (p < 0.0001)	0.440 (p < 0.0001)	11.1 vs. 5.6 (p = 0.0114)	0.554 (p = 0.0135)
Non-tBRCA LOH- (rucaparib n = 107; placebo n = 54)	6.7 vs. 5.4 (p = 0.0040)	0.583 (p = 0.0049)	8.2 vs. 5.3 (p = 0.0002)	0.470 (p = 0.0003)

Abbreviations: HRD = homologous recombination deficiency; IRR = independent radiology review; ITT = intent-to-treat; LOH = loss of heterozygosity; non-tBRCA LOH+ = patients without a deleterious tBRCA mutation and with percent of tumor genome LOH ≥ 16%; non-tBRCA LOH- = patients without a deleterious tBRCA mutation and with percent of tumor genome LOH < 16%; PFS = progression-free survival; tBRCA- = tumor tissue mutation in BRCA1 or BRCA2, includes germline BRCA and somatic BRCA mutations.

[a] Stratified log-rank analysis.

[b] Cox proportional hazard model.

1.3.2.2.3 OVERVIEW OF SAFETY

Results of an integrated safety analysis for rucaparib treatment in over 1,000 patients with ovarian or prostate cancer who received 600 mg BID rucaparib 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, and constipation), asthenia/fatigue, anemia/decreased hemoglobin, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, decreased appetite, and dysgeusia. The most common TEAEs ≥ Grade 3 included anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue.

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 in either the treatment or maintenance settings 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) and few patients discontinued rucaparib due to ALT/AST elevations.[13,16] Similarly, elevations in creatinine were self-limiting and stabilized over time. 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.[13,16] Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters (Section 1.3.2.1). 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 (AESIs), 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, as well as a deleterious BRCA mutation.[39,40] 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 for rucaparib is provided in the rucaparib IB.

1.4 Rationale for this Study of Rucaparib

Patients with MIBC represent a population with advanced disease, poor prognosis, and unmet need. The median OS in this patient population is 15 months. Response rates to initial treatment with cisplatin-based chemotherapy range from 49% to 72%; however, most patients will have disease relapse within 9 months following initial treatment.[4,5] Furthermore, the majority of patients will progress within 2 to 3 months following failure on first- and/or second-line therapy.[6] There are limited treatment options beyond first- or second- line treatment with platinum-containing chemotherapy and/or an immune checkpoint inhibitor, therefore additional therapies for the treatment of patients with MIBC beyond first- or second-line are needed. Treatment within clinical studies is considered an appropriate treatment option for these patients.[18]

Homologous recombination pathway defects may be responsible for the genetic instability observed in many cancers including ovarian cancer and urothelial cancer. For ovarian cancer, it is estimated approximately 50% of high-grade serous ovarian cancer patients have alterations in HRR genes.[41] Clinical data with rucaparib have shown patients with and without a BRCA (germline or somatic) mutation benefit from rucaparib treatment in both the treatment and maintenance settings of ovarian cancer.[16,31] While patients with a BRCA

mutation derived the most benefit, patients without evidence of a BRCA mutation also derived significant benefit suggesting an incomplete understanding of biomarkers involved in sensitivity to a PARP inhibitor.[16] Similar to ovarian cancer, an analysis of TCGA bladder cancer data set (http://cancergemone.nih.gov) indicates that approximately 60% of bladder cancer tumors may have alterations in HRR genes and/or other genomic/epigenetic deficits that can drive HRD (Clovis, data on file). The presence of HRD in tumors has been demonstrated to predict response to cisplatin-based chemotherapy in bladder cancer.[10,11] Based on these analyses and data, bladder cancer patients have the potential to benefit from treatment with a PARP inhibitor.

The purpose of this study is to assess the efficacy and safety of rucaparib in patients with locally advanced unresectable or metastatic urothelial bladder cancer. The study will enroll approximately 200 patients, regardless of HRD status, who have received 1 or 2 prior treatment regimens. Enrollment of patients, regardless of HRD status, who have received ≤ 2 prior treatments, is appropriate given that available treatment options are limited and both HRD-positive and HRD-negative patients may potentially respond to treatment with rucaparib. Primary efficacy will be assessed in a prospectively defined HRD-positive population as well as the intent-to-treat (ITT) population. Additional secondary and exploratory efficacy and safety endpoints will also be evaluated in HRD subgroups and the ITT population.

2 STUDY OBJECTIVES AND ENDPOINTS

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

Table 2. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
To evaluate objective response rate (ORR) in molecularly-defined homologous recombination deficiency (HRD)-positive and intent-to-treat (ITT) populations using a prospectively defined molecular signature.	ORR per Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1 (v1.1), as assessed by investigator, in HRD-positive and ITT populations
Secondary Objectives	**Secondary Endpoints**
To evaluate duration of response (DOR)	DOR per RECIST v1.1, as assessed by investigator
To estimate progression-free survival (PFS)	Disease progression according to RECIST v1.1, as assessed by the investigator, or death due to any cause
To estimate overall survival (OS)	OS
To evaluate safety and tolerability of rucaparib	Incidence of adverse events (AEs), clinical laboratory abnormalities, changes in ECGs and vital signs, and dose modifications
To evaluate steady-state pharmacokinetics (PK) of rucaparib	Trough (C_{min}) level rucaparib concentrations
Exploratory Objectives	**Exploratory Endpoints**
To assess biomarkers that correlate with response to rucaparib	Biomarkers correlated with response to rucaparib
To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to rucaparib	Association of cancer-related mutations detected in baseline ctDNA samples with response to rucaparib
To assess molecular changes over time in plasma and tumor samples	Association of changes in cancer-related mutations detected in plasma and tissue samples over time with response to rucaparib
To evaluate biomarkers associated with resistance to rucaparib	Biomarkers associated with resistance to rucaparib

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2 multicenter, open-label study evaluating rucaparib for treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma. This study will enroll patients with measurable disease per RECIST v1.1. All patients must have received 1 or 2 prior treatment regimens and have radiologic progression during or after the most recent regimen. Patients who have received prior PARP inhibitor treatment will be excluded. Tumor tissue will be analyzed to determine the percentage of genomic LOH[31] and patients will be classified as HRD-positive or HRD-negative for efficacy analyses based on a prespecified LOH cut-off defined in the statistical analysis plan (SAP).

This study consists of a Screening Phase (Section 3.1.1), a Treatment Phase (Section 3.1.2) and a Post-treatment Phase (Section 3.1.3). Patients will receive rucaparib monotherapy in the Treatment Phase, and will undergo procedures and assessments including regular safety and efficacy evaluations during the entire conduct of the study.

3.1.1 Screening Phase

After providing consent to participate, patients will undergo procedures and assessments as described in Section 7.3 within 28 days prior to the first dose of rucaparib. During this period, unless otherwise required by local regulations, only adverse events (AEs) which are related to protocol-mandated assessments will be reported.

During the Screening Phase, each patient, with the following exceptions, will undergo a biopsy for collection of tumor tissue. Tumor tissue samples should be from primary or metastatic soft tissue tumor (see Section 7.6.5.1 for details). Patients who had tumor tissue collected as part of standard of care ≤ 6 months prior to the first planned dose of rucaparib and had no intervening anti-cancer treatments during this period are not required to have a biopsy provided that adequate tumor tissue can be provided for analysis. Whenever possible, submission of additional archival tumor tissue (with no limit on date of collection) is strongly encouraged. If tissue is unable to be submitted prior to the first dose, it must be submitted to the sponsor's central laboratory by Cycle 2 Day 1. Tumor tissue will be analyzed for HRD signature status. 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 detected from this testing, the finding will be made available to the investigator provided the results are generated from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and the patient has consented to receive the results.

Additional screening assessments will include collection of the patient's medical information and demographics, prior anti-cancer treatments, prior and current medications and procedures, physical exam, vital signs, 12-lead ECG, ECOG performance status, laboratory safety assessments, urinalysis, serum pregnancy tests (for women of child-bearing potential only), and tumor assessments by computed tomography (CT) scans or magnetic resonance imaging (MRI) scans (if required by local authorities) and a baseline biomarker blood sample for circulating cell-free tumor DNA (ctDNA) analysis as described in Section 7.3.

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

- details of prior therapy for locally advanced unresectable or metastatic urothelial carcinoma
- screening laboratory assessments

3.1.2 Treatment Phase

Rucaparib will be administered at a starting dose of 600 mg BID. During the Treatment Phase, patients will undergo procedures and assessments including regular evaluations for safety and efficacy as described in Section 7.4. A blood sample will be collected on Cycle 1 Day 1 and stored for subsequent genomic DNA testing and exploratory analysis. Blood for ctDNA analysis will be collected before dosing on Day 1 of Cycles 1, 2, 3, and at every 8 weeks thereafter coinciding with radiographic scans.

Tumor assessments by CT will be performed at the end of every 8 calendar weeks (±7 days) from Cycle 1 Day 1 up to 18 months and every 12 calendar weeks (±7 days) thereafter, and at the End of Treatment Visit, if applicable. RECIST v1.1 criteria will be used to document radiologic response. MRI scans may be performed in place of CT scans if required by local authorities. Any drug modifications (interruption, dose reduction, or discontinuation) should be documented in the electronic Case Report Form (eCRF) and source documents. If study treatment is interrupted, tumor assessments will not be delayed and will be performed on the regular study schedule. Copies of all radiologic scans (and other imaging, as appropriate) will be collected.

Patients will receive rucaparib until confirmed radiologic disease progression assessed by investigator based on RECIST v1.1, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, death, or withdrawal of consent. Palliative radiation therapy on lesions not considered target lesions for RECIST v1.1 assessments is allowed and should not result in discontinuation of rucaparib therapy. Patients who discontinue study treatment for reasons other than radiologic disease progression or death, should continue radiologic tumor assessment performed as described in Section 3.1.3.

If a patient has radiologic progression per RECIST v1.1, but is deriving clinical benefit in the opinion of the investigator, then continuation of treatment beyond progression is allowed per Section 5.4.3. In such cases, the decision to continue treatment should be documented in the source documents and the patient must provide additional consent prior to continuing treatment with rucaparib. These patients will continue to undergo all protocol required assessments specified in Table 5.

Patient safety will be monitored on a regular basis using procedures and assessments described in Section 7 and Section 11.4. Safety data will be periodically reviewed by the Data Monitoring Committee (DMC) as described in Section 11.6. The DMC will comprise coordinating investigators and sponsor representatives. The DMC will meet after the first 20 patients received rucaparib for at least 1 cycle or discontinued study treatment and approximately every 6 months thereafter until completion of the study.

3.1.3 Post-treatment Phase

The sponsor or designee should be notified of all treatment terminations as soon as possible. The date and reason for cessation of rucaparib must be documented in the eCRF and source documents. Patients will undergo procedures and assessments during the Post-treatment Phase as described in Section 7.5. Upon treatment discontinuation, patients will have an End of Treatment Visit (Section 7.5.1), a 28-day Follow-up Visit (Section 7.5.2), and then will proceed to long-term follow-up (Section 7.5.3).

All patients enrolled into the study will provide an End of Treatment Visit blood sample for ctDNA analysis. An optional tumor biopsy will be collected prior to the start of subsequent anti-cancer therapy from patients who experience radiographic or unequivocal clinical disease progression and who provide additional consent.

For patients who had their last tumor assessment ≥ 8 weeks prior to End of Treatment Visit, a tumor assessment must be performed.

If treatment was discontinued for reasons other than radiologic disease progression or death, radiologic tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan]) will continue until confirmed radiographic disease progression by RECIST v1.1 criteria as assessed by the investigator, loss to follow-up, withdrawal of consent, death, initiation of subsequent treatment, or study closure. For these patients, tumor assessments should continue to be performed at the end of every 8 calendar weeks (±7 days) relative to Cycle 1 Day 1 up to 18 months and then every 12 calendar weeks (±7 days) thereafter, until confirmed radiologic disease progression by RECIST v1.1 criteria as assessed by the investigator, loss to follow-up, withdrawal of consent, death, or study closure.

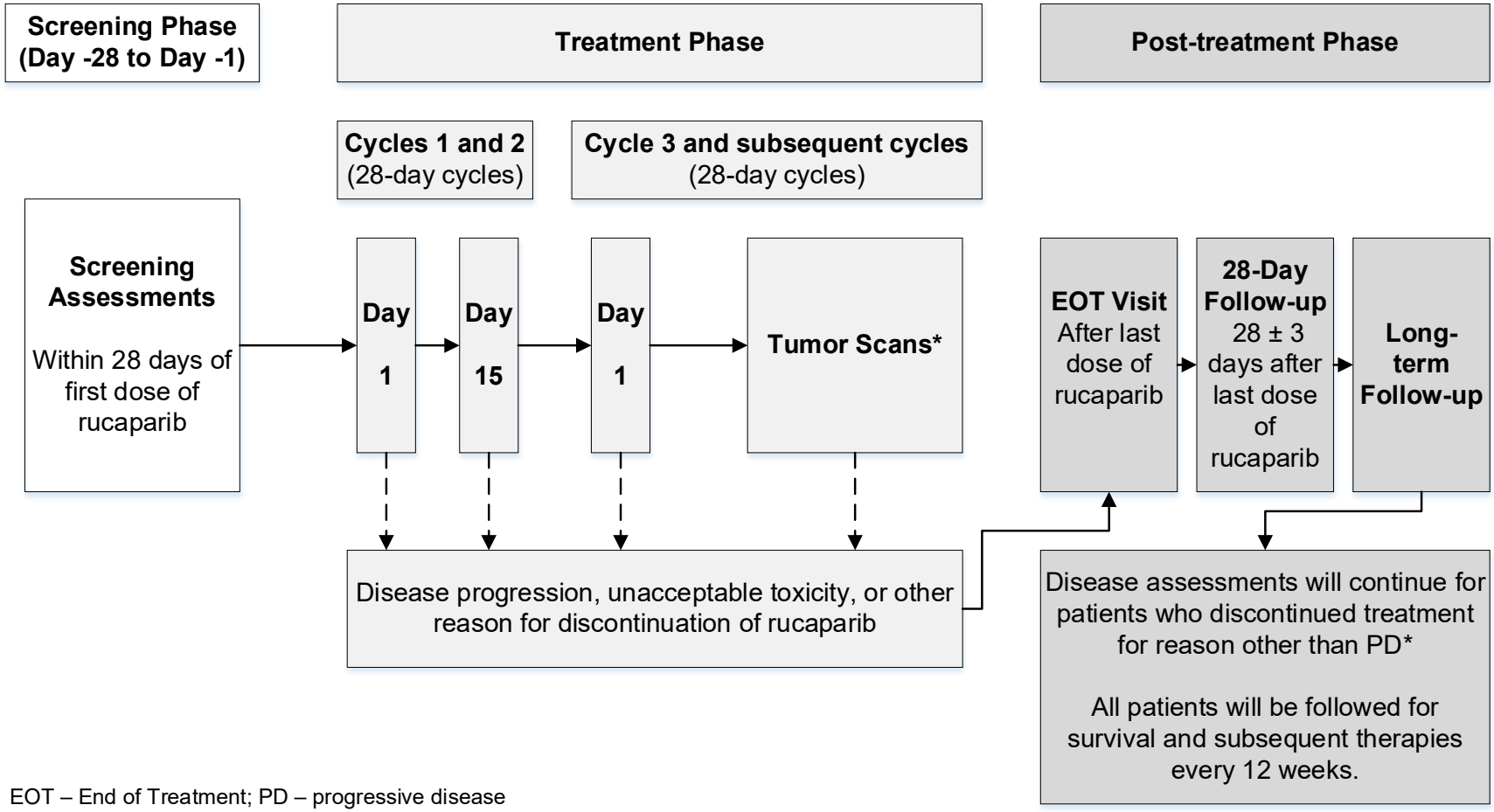
Ongoing serious adverse events (SAEs), AESIs, and treatment-related Grade 3/4 AEs will be followed until either resolution or stabilization has been determined or until loss to follow-up. After the 28-day Follow-up Visit, related SAEs and all AESIs (irrespective of causality) need to be reported.

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

3.2 Study Schema

The study schema is provided in Figure 1.

Figure 1. Study Schema



EOT – End of Treatment; PD – progressive disease
* Tumor scans every 8 calendar weeks (± 7 days) from Cycle 1 Day 1 up to 18 months then every 12 calendar weeks (± 7 days) thereafter

3.3 End of Study

The study will close when all enrolled patients have discontinued treatment and completed the 28-day Follow-up Visit, and the long-term follow-up, as applicable. If the study is closed for any other reason, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of entering an extension protocol in which they can continue to receive rucaparib.

The sponsor may discontinue the study early for any reason as noted in Section 11.7.

4 STUDY POPULATION SELECTION

4.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 200 patients.

Patients will be enrolled at approximately 65 sites worldwide.

4.2 Inclusion Criteria

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

1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the Informed Consent Form (ICF) is signed.
3. Have histologically or cytologically confirmed locally advanced unresectable (tumor, node, metastasis [TNM] staging of T4b and any N; or any T and N2-3) or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureter, urinary bladder, or urethra). Mixed transitional/non-transitional cell histologies are allowed.
4. Received 1 or 2 prior treatment regimens (eg, cisplatin- or carboplatin-containing chemotherapy, immune checkpoint inhibitor, and/or clinical trial) for locally advanced unresectable or metastatic disease and had confirmed radiologic disease progression during or following the most recent treatment. The principal investigator is responsible for ensuring the patient has received anti-cancer treatment as appropriate in the country of enrollment, taking into account the patient's current health status as well as how the patient responded to/tolerated prior treatment(s).
    a. Neoadjuvant and/or adjuvant treatment for muscle invasive disease will be considered a treatment regimen if radiologic disease progression occurred ≤ 12 months from the completion of treatment.
    b. No more than 1 prior platinum-containing systemic chemotherapy regimen for advanced disease is permitted. A change of platinum chemotherapy within the same treatment regimen will be considered 1 prior platinum-containing chemotherapy. Platinum-containing chemotherapy given as radio-sensitization combined with radiation therapy to control locally advanced disease will not be considered as a prior regimen of systemic therapy.
    c. For patients who have never received platinum, the patient must currently be ineligible for or refuse cisplatin treatment.
    d. A treatment regimen that is held for reasons other than progression which is subsequently resumed at a later date with no other intervening systemic anti-cancer treatment is considered 1 treatment regimen.
5. Mandatory tumor tissue must be collected ≤ 28 days prior to the first dose of rucaparib treatment. A biopsy or surgical resection of tumor tissue is required, unless archival tumor tissue collected ≤ 6 months prior to the first dose of rucaparib is

available and no intervening anti-cancer treatments were administered during this period. Tumor tissue should be of adequate quality for molecular profiling.(See Section 7.6.5.1)

6. Have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1). A measurable tumor lesion in a previously irradiated site is acceptable if subsequent progression has been demonstrated in that lesion.
7. Have adequate organ function confirmed by the following laboratory values obtained ≤ 14 days prior to first dose of rucaparib:
    a. Bone Marrow Function
        i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
        ii. Platelets > 100×10^9/L
        iii. Hemoglobin ≥ 9 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
    c. Renal Function
        i. Measured or calculated creatinine clearance (CrCL) ≥ 30 mL/min or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. For calculated CrCL or eGFR, the Cockcroft Gault formula or institutional standard formula can be used.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 14 days prior to first dose of rucaparib.
9. Have life expectancy ≥ 12 weeks.

4.3 Exclusion Criteria

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

1. Active second malignancy for which patient has received treatment within 2 years prior to the first dose of rucaparib with exception for the following circumstances:
    a. Curatively treated non-melanoma skin cancer.
    b. Non-invasive diseases such as low risk cervical cancer or any cancer in situ.
    c. Localized (early stage) cancer treated with curative intent (without evidence of recurrence and intent for further therapy) and in which no systemic therapy was indicated.
2. Prior treatment with a PARP inhibitor.

3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks prior to the first dose of rucaparib.
4. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib.
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C.
6. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib.
    b. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to the first dose of rucaparib. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
    c. Male patients who refuse to use condoms during sex. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib.
7. Received anti-cancer treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of rucaparib and/or ongoing treatment-related adverse events National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) > Grade 1 except for neuropathy, ototoxicity, alopecia, and electrolyte abnormalities.
8. Non-study 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.
9. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

4.4 Patients or Partners of Patients with Reproductive Potential

Pregnancy is an exclusion criterion. Women of childbearing potential or male patients of reproductive potential with female partners of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least 6 months after the last dose of rucaparib or longer if requested by local authorities.

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib. In addition, a serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase and at the time of treatment discontinuation. Pregnancy testing will be conducted locally.

Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib.

Male patients are required to use a condom during sex with a partner to avoid the possibility of exposure of the partner to rucaparib, regardless of whether the partner is a woman of childbearing potential or not. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib.

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

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

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy; or
- 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.

Female and male patients of reproductive potential must practice highly effective methods (failure rate < 1% per year) of contraception with their partners, if of reproductive potential, during treatment and for 6 months following the last dose of rucaparib or longer if requested by local authorities. Highly effective contraception includes:

- Ongoing use of progesterone only injectable or implantable contraceptives;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable; or
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib.

4.5 Compliance with Inclusion/Exclusion Criteria

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

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s) and Storage

This study will assess the investigational drug rucaparib.

Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338-BW and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of the investigational product is provided below with details in the Pharmacy Manual.

Table 3. Description of Investigational Product

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation: (strengths expressed as free base)	Tablet; film-coated; 200 mg (blue, round, debossed with C2), 250 mg (white, rounded diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3)
How Supplied:	200 mg, 250 mg, 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:	As directed on the product label

Abbreviation: INN = International Nonproprietary Name

5.2 Packaging and Labeling

5.2.1 Rucaparib

All tablets are provided in high-density polyethylene (HDPE) bottles (or equivalent) with child-resistant caps and should be stored in the provided containers and as directed on the product label. Patients may be dispensed 1 or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days of treatment (plus a 2-day overage) until the next rucaparib dispensation visit.

Bottles containing rucaparib tablets will be labeled according to national regulations for investigational products.

5.3 Method of Assigning Patients to Treatment Groups

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

5.4 Preparation and Administration of Protocol-specified Treatment

The starting dose of rucaparib is 600 mg ingested BID. Patients may take rucaparib with or without food. Each dose should be taken with water. Tablets should be swallowed whole

without crushing or chewing. Tablet strength combinations shall be determined by the Interactive Web Response System (IWRS).

Patients should take rucaparib doses as close as possible to 12 hours apart, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

Dosing with rucaparib may be held or reduced as described in Section 5.4.1.

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

5.4.1 Rucaparib Dose Modification Criteria

5.4.1.1 Treatment Interruption Guidelines

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

- Grade 3 or 4 hematologic toxicity. Anemia should be managed as described below (Section 5.4.1.2)
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below (Section 5.4.1.3)
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity improves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed and documented between the investigator and the sponsor.

5.4.1.2 Management of Anemia including Evaluation for MDS/AML and Follow-up of Patients who Discontinue Treatment with Ongoing Anemia:

- If the patient develops anemia CTCAE Grade ≥ 3, rucaparib treatment should be held until the anemia improves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.
- If the duration of dosing is interrupted for > 14 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed and documented between the investigator and the sponsor or designee.
- In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event.
- If, after 42 days of interruption of rucaparib, the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
- The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

5.4.1.3 Management of Rucaparib Treatment-Emergent ALT/AST Elevations:

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

Drug-induced liver injury (DILI) is described in the US FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation[42] and should be referenced when managing treatment-emergent ALT/AST elevations.

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

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

While treatment is interrupted, the patient should be evaluated 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 international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, rucaparib must be permanently discontinued.

All cases of possible DILI will 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.

5.4.1.4 Rucaparib Dose Reduction Steps

Dose reduction steps are presented in Table 4.

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

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

Table 4. Rucaparib Dose Reduction Steps

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

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

5.4.2 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.

5.4.3 Treatment with Rucaparib beyond Disease Progression

Patients will receive rucaparib until confirmed radiologic disease progression as assessed by investigator using RECIST v1.1 criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, death, or withdrawal of consent. If a patient receiving rucaparib has met criteria for confirmed radiologic disease progression by RECIST v1.1 criteria, but the patient continues to derive clinical benefit in the opinion of the investigator, then continuation of treatment will be permitted. In such cases, the investigator's decision to continue treatment should be documented in the source documents and the patient must provide additional consent prior to continuing treatment with rucaparib. Clinical scenarios where continuation of rucaparib treatment after radiographic progression may be considered include 1) a patient for whom radiographic progression develops slowly while disease-related symptoms remain well controlled, 2) a patient who experiences progression in a site of disease that is unlikely to adversely affect prognosis (eg, enlargement of a solitary lymph node), or 3) a patient with general disease control but limited progression in sites of disease that can be managed with local therapies such as surgery or radiation. Patients continuing to receive rucaparib will continue to have all protocol-required assessments as described in Section 7.

5.5 Blinding/Masking of Treatment

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

5.6 Treatment Compliance

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

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

5.7 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of rucaparib receipt, dispensation, use, return, destruction, and reconciliation for rucaparib provided by the sponsor. An IWRS will be used to manage rucaparib inventory at all sites. In order to function properly, the system will

require real-time entry of rucaparib receipt, dispensation, destruction, patient treatment discontinuation, etc. by study personnel at the study site.

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

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

6 PRIOR AND CONCOMITANT THERAPY

Patients who have received prior treatment with a PARP inhibitor including intravenous (IV) or oral rucaparib are not eligible to participate in this study.

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

6.1 Supportive Care

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

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 Radiotherapy

Palliative radiotherapy on lesions not considered target lesions for tumor evaluation per RECIST v1.1 is permitted during the study. Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation related toxicity.

6.3 Anti-cancer or Experimental Therapy

No other anti-cancer therapies (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind, with the exception of palliative radiotherapy, will be permitted while the patient is participating in the study. Prior treatment with anti-cancer therapies must have been completed > 14 days prior to the first dose of rucaparib.

6.4 Cytochrome P450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medicines that are sensitive clinical substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A (Appendix 3). Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers. Selection of an alternative concomitant medication is recommended.

6.5 Anticoagulants

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

6.6 Other Concomitant Medications

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

Rucaparib marginally increased digoxin area under the plasma concentration-time curve (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 MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC_{50}) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

7 STUDY PROCEDURES AND ACTIVITIES

7.1 Schedule of Assessments

Table 5 summarizes the procedures and assessments to be performed for all patients. Study procedures and assessments should be performed as close to the scheduled time as possible, but within ±3 days of the scheduled time unless otherwise stated. Tumor assessment visits are scheduled relative to Study Day 1.

Table 5. Schedule of Assessments

	Screening Phase	Treatment Phase[a] (±3 days of scheduled timepoint)			Post-treatment Phase		
		Cycles 1 and 2		Cycle 3+			
Procedure	**Day -28 to Day -1**	**Day 1[b,c]**	**Day 15[c]**	**Day 1[c]**	**End of Treatment Visit**	**28-day Follow-up Visit (28 ±3 days after last dose)**	**Long-term Follow-up**
Informed Consent[d]	X						
Medical/Oncology History[e]	X						
Physical Examination[f], Height[f], Weight	X	X	X	X	X	X	
ECOG Performance Status	X[g]	X		X	X	X	
Vital Signs	X	X[h]	X[h]	X[h]	X	X	
Adverse Events[i]	X	X	X	X	X	X[i]	X[i]
Prior/Concomitant Medications and Procedures	X	X	X	X	X	X	
12-lead ECG[j]	X				X		
Hematology[k] (local lab)	X[g]	X	X	X	X	X	
Serum Chemistry[l] (local lab)	X[g]	X	X	X	X	X	
Serum Pregnancy Test[m] (local lab)	X[g]	X		X	X		
Urinalysis[n] (local lab)	X[g]	X	X	X	X	X	
Disease Assessment/Tumor Scans[o,p]	X			X[p]	(X)[q]	X[r]	X[r]
Tumor Tissue Biopsy/Resection/Sample	X[s]				(X)[t]		
Archival Tumor Tissue	(X)[u]						
ctDNA Blood Sample[v] (central lab)	X	X		X[w]	X	X	
Blood Sample for Genomic Analysis (central lab)		X[x]					
Rucaparib Dispensation/Administration/Accountability		X	X	X	X		
Plasma PK Sample[y] (central lab)		X[z]		X[z]			
Survival and Subsequent Treatments							X[aa]

Table 5. Schedule of Assessments

Abbreviations: AE(s) = adverse event(s); AESI(s) = adverse events of special interest; ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BRCA = breast cancer gene; BUN = blood urea nitrogen, CO_2 = carbon dioxide; CR = complete response, CrCL = creatinine clearance; CT = computed tomography, ctDNA = circulating cell-free tumor DNA; ECG(s) = electrocardiogram(s), ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; FFPE = formalin-fixed, paraffin-embedded; gBRCA = germline mutation in BRCA; ICF = Informed Consent Form; LDH = lactate dehydrogenase, MCH = mean corpuscular hemoglobin, MCHC, = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response or PR interval, QRS = QRS complex/interval; QT = QT interval; RBC = red blood cell, RECIST = Response Evaluation Criteria in Solid Tumors; SAE(s) = serious adverse event(s), WBC = white blood cell

a	=	Treatment cycles are 28 days. Unless otherwise specified, all assessments are to be completed within ±3 days of scheduled time point.
b	=	Any procedures required on Cycle 1 Day 1 may be omitted if completed ≤ 3 days prior to first dose of rucaparib.
c	=	Patients are to refrain from taking their first dose of rucaparib at home on these days. Procedures are to be completed before rucaparib is administered.
d	=	Consent may be completed outside the 28-day screening window as consent does not expire. Reconsent is not required if outside the screening window.
e	=	Patient's medical record must include prior treatments received, dates of administration, date of progression, and radiology report(s) to support assessment of disease progression. gBRCA test results, if known, will also be captured.
f	=	A complete physical exam should be performed at Screening and End of Treatment Visits; a limited physical exam may be performed at all other visits. Height at screening only.
g	=	To be performed ≤ 14 days prior to the first dose of rucaparib. Serum pregnancy test to be performed ≤ 3 days prior to the first dose of rucaparib, if applicable.
h	=	Vital signs (blood pressure, pulse, and temperature) to be taken on clinic visit days.
i	=	AEs (inclusive of SAEs and AESIs) occurring after first dose of rucaparib through 28 days after last dose of rucaparib will be recorded. In addition, SAEs occurring after signing of the ICF and that were related to a screening procedure will also be reported. Ongoing SAEs, AESIs, and treatment-related Grade 3/4 AEs will be followed to resolution or stabilization, death, or until lost to follow-up. Only related SAEs and AESIs (regardless of causality) will be reported after the 28-day Follow-up Visit.
j	=	Heart rate, PR, QRS, QT, and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.
k	=	Includes RBC count and parameters (hemoglobin, hematocrit, MCV, MCH, MCHC), reticulocyte count, WBC count, and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and results must be reviewed by the investigator prior to the first dose of rucaparib. Additional and more frequent tests may be performed at the investigator's discretion.
l	=	Includes total protein, albumin, measured or calculated CrCL or eGFR (for CrCL calculation or eGFR, the Cockcroft Gault formula or institutional standard formula can also be used), BUN or urea, total bilirubin, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride, CO_2, calcium, phosphorus, and total cholesterol. Total cholesterol testing does <u>not</u> require fasting. Blood will be analyzed by a local laboratory and results must be reviewed by the investigator prior to the first dose of rucaparib. Additional and more frequent tests may be performed at the investigator's discretion.

Table 5. Schedule of Assessments

m	=	Women of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of rucaparib. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond during the Treatment Phase. A serum pregnancy test must be performed at the End of Treatment Visit.
n	=	Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal, perform microscopic evaluation.
o	=	Disease assessment to include clinical examination and appropriate imaging techniques, including CT scans of the chest, abdomen, and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. MRI may be used in place of CT scans if required by local authorities. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment. Copies of CT scans will be collected from all patients. Independent radiology review may be conducted on all or a subset of CT or MRI scans.
p	=	Tumor scans to be performed at the end of every 8 calendar weeks (±7 days) during the Treatment Phase. A confirmatory scan should be performed ≥ 4 weeks after an initial response of PR or CR is observed. Patients who have been on study at least 18 months, may decrease the frequency of disease assessments to every 12 calendar weeks (±7 days).
q	=	Disease assessments should also be done at the time of treatment discontinuation if it has been ≥ 8 weeks since the last assessment.
r	=	If treatment was discontinued for reasons other than radiologic disease progression or death, radiologic tumor assessment (using the same methodology as was used at initial study screening) will continue until confirmed radiographic disease progression by RECIST v1.1 (as assessed by the investigator), loss to follow-up, withdrawal, death, initiation of subsequent treatment, or study closure.
s	=	A biopsy or resection of tumor tissue must be collected ≤ 28 days prior to first dose of rucaparib. Alternatively, tumor tissue collected ≤ 6 months prior to the first dose of rucaparib may be submitted, provided there have been no intervening anti-cancer treatments during this period and the tissue is of adequate quality. Tumor tissue must be obtained from a soft tissue tumor lesion; ascites is not acceptable. Refer to the Pathology Charter for detailed sample handling instructions.
t	=	An optional post-treatment tumor biopsy sample may be collected from patients who progress on rucaparib. If the progression is due to new lesions, the preference is to obtain the biopsy from the new lesion(s). Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions.
u	=	Archival FFPE tumor tissue must be submitted if available. Refer to the Pathology Charter for detailed sample handling instructions.
v	=	Refer to the Laboratory Manual for detailed sample processing instructions. Cycle 1 ctDNA must be collected even if within 3 days of screening ctDNA.
w	=	To be performed at the time of tumor evaluation for Cycle 3 and in subsequent cycles coinciding with tumor scans through the 28-day Follow-up Visit.
x	=	Cycle 1 Day 1 only
y	=	A single sample should be collected as close as possible to 12 hours after the last dose has been taken and prior to the next dose. Refer to the Laboratory Manual for sample processing instructions.
z	=	Cycles 2, 3, and 4 only.
aa	=	All patients discontinued from treatment, regardless of reason, should be followed for survival and subsequent therapies every 12 weeks until death, loss to follow-up, withdrawal of consent from study, or study closure, whichever happens first. Follow-up can be performed via the telephone.

7.2 Informed Consent

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 prior to any study activities. The information on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved consent form should be translated and communicated in the language the patient (or legally authorized representative [where acceptable according to national law and/or local regulations]) can understand.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiologic disease progression/treatment discontinuation must provide additional consent for this procedure.

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

Analyses of blood sample for genomic analysis, plasma ctDNA, and tumor tissue will be performed by the sponsor-selected central laboratory.

The patient will have the option to provide additional consent to allow or not allow the sponsor to retain residual samples for future unspecified research.

All procedures and assessments are to be completed within ±3 days of the scheduled time unless otherwise stated.

7.3 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to enrollment within the allowable windows of time as indicated below. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care. Screening procedures may be repeated if the findings/results are considered invalid or not representative of the patient's baseline medical status. When screening procedures are repeated, the rationale should be documented in the source file. Consent may be completed outside the 28-day screening window as consent does not expire. Reconsent is not required if outside the screening window.

7.3.1 Up to 28 days Prior to Start of Treatment

- Medical/oncology history, including demographic information
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and body temperature)
- Serious adverse event (SAE) monitoring (only report if related to screening procedure)
- Prior and concomitant medications, any surgical/medical procedures
- 12-lead ECG

- Tumor assessment: assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1). The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study.
  - If a patient has known brain metastases, this disease should be evaluated at each required assessment time
- Tumor tissue from a primary tumor or a metastatic disease site in the form of a formalin-fixed paraffin-embedded (FFPE) block or unstained slides (required). (See Section 7.6.5.1)
- Archival FFPE tumor tissue (if available) (See Section 7.6.5.2)
- Collect ctDNA blood sample

7.3.2 Up to 14 days Prior to Start of Treatment

- ECOG performance status (Appendix 2)
- SAE monitoring (only report if related to screening procedure)
- Hematology
- Serum chemistry. Note: fasting is not required
- Urinalysis (performed on freshly voided clean sample)
- Serum pregnancy test for women of childbearing potential (must be completed ≤ 3 days prior to the first dose of rucaparib)

7.4 Treatment Phase

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

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

7.4.1 Cycle 1 Day 1

The following procedures will be completed before rucaparib is administered, unless if completed ≤ 3 days prior to the first dose of rucaparib in which case they may be omitted:

- Physical examination
- Weight
- ECOG performance status (Appendix 2)

- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology
- Serum chemistry (fasting is not required)
- Serum pregnancy test for women of childbearing potential
- Urinalysis
- Collect ctDNA blood sample (this sample **must** be collected even if a sample was collected within 3 days prior to the first dose of rucaparib)
- Blood sample for genomic analysis
- Adverse event (AE) monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability
- Dispensation of rucaparib

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until the next rucaparib dispensation visit, with a small overage. Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.4.1.

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

7.4.2 Cycle 1 Day 15

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

The following procedures will be completed before rucaparib is administered:

- Physical examination
- Weight
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis

- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.4.1.

7.4.3 Cycle 2 Day 1

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

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

The following procedures will be completed before rucaparib is administered:

- Physical examination
- Weight
- ECOG performance status (Appendix 2)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology
- Serum chemistry (fasting is not required)
- Serum pregnancy test for women of childbearing potential
- Urinalysis
- Collect ctDNA blood sample
- Collect plasma sample for PK analyses
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability
- Dispensation of rucaparib

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.4.1.

7.4.4 Cycle 2 Day 15

The following procedures will be completed before rucaparib is administered:

- Physical examination
- Weight
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.4.1.

7.4.5 Cycle 3 Day 1 and Every Cycle Thereafter

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

Plasma samples for PK analysis should be collected before the morning dose on Cycle 3 Day 1 and Cycle 4 Day 1, as close as possible to 12 hours after the previous dose. If the start of the next dose is delayed, the PK sample should still be collected during this visit instead of the delayed start of the next study visit;

The following procedures will be completed before rucaparib is administered:

- Physical examination
- Weight

- ECOG performance status (Appendix 2)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Tumor assessment scans at the end of every 8 calendar weeks (±7 days) from the first dose of rucaparib for the first 18 months of treatment, and then every 12 calendar weeks (±7 days) thereafter
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Collect ctDNA blood sample (at time of tumor assessment scans)
- Collect plasma sample for PK analyses (Cycle 3 Day 1 and Cycle 4 Day 1 only)
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for accountability
- Dispensation of rucaparib

Patients will ingest rucaparib twice daily at about the same times every day as close as possible to 12 hours apart. Rucaparib should be taken with water and with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) and return with them to the study site for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described in Section 5.4.1.

7.5 Post-treatment Phase

7.5.1 End of Treatment Visit

Upon treatment discontinuation, regardless of the reason, patients will have an End of Treatment Visit. For patients that have radiologic disease progression by RECIST v1.1, but continue to derive benefit in the opinion of the investigator, they will be allowed to continue treatment in the Treatment Phase. In such cases, the investigator's decision to continue treatment should be documented in the source documents and the patient must provide additional consent prior to continuing treatment with rucaparib as described starting in Section 7.4.5 and an End of Treatment Visit will occur at the end of all rucaparib treatment. Patients who continue treatment with rucaparib after radiologic disease progression will have the option of tumor tissue biopsy collection at time of first disease progression on study (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

The following procedures will be performed at the End of Treatment Visit:

- Physical examination
- Weight
- ECOG performance status (Appendix 2)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- 12-lead ECG
- Tumor assessment/ scans if it has been ≥ 8 weeks since the last assessment
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Collect ctDNA blood sample
- AE monitoring
- Patients return all unused tablets and containers (empty, partially used, and/or unopened) to the study site for final accountability.
- Optional tumor tissue biopsy collection after the time of disease progression (radiologic or clinical) and prior to initiation of any subsequent anti-cancer therapy (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

7.5.2 28-day Follow-up Visit

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

- Physical examination
- Weight
- ECOG performance status (Appendix 2)
- Vital signs
- Concomitant medications and any surgical/medical procedures
- Tumor assessment only for those patients that have not had radiographic progression confirmed by investigator assessment
- Hematology
- Serum chemistry (fasting is not required)
- Urinalysis

- Collect ctDNA blood sample
- AE monitoring
- Information collected for subsequent treatments and adverse event of special interest (AESI) will require appropriate documentation (ie, laboratory and/ or pathology reports) and should be reported as indicated in Section 8.9.

Patients who do not withdraw from the study at this visit will continue with long-term follow-up as described in Section 7.5.3.

7.5.3 Long-term Follow-up

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

- If applicable, tumor assessment (using the same methodology as was used at initial study screening [eg, CT scan or MRI scan if required by local authorities]) when the reason for treatment discontinuation was other than death or disease progression based on radiologic assessment and it has been ≥ 8 weeks since last scan or disease progression was noted on the last scan. Tumor assessment should continue to be performed at the end of every 8 calendar weeks (±7 days) relative to Cycle 1 Day 1 up to 18 months, then every 12 calendar weeks (±7 days), until confirmed radiologic disease progression by RECIST v1.1 criteria as assessed by the investigator, loss to follow-up, withdrawal, death, initiation of subsequent treatment, or study closure.
- All patients discontinued from treatment, regardless of reason, will be followed and information collected for subsequent treatments and survival every 12 weeks from last dose of rucaparib until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone and can be completed to coincide with scheduled tumor assessments.
- SAEs related to rucaparib and all AESIs, irrespective of causality, are to be reported as specified in Section 8.9.

7.6 Methods of Data Collection

7.6.1 Medical History and Demographic/ Baseline Characteristics

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

The patient's entire oncology history will be collected on the appropriate eCRF including date of diagnosis for urothelial carcinoma (and other malignancy, if applicable), prior surgeries/treatments received for cancer, dates of treatment administration, best response

achieved, date of progression and how assessed, and BRCA or other HRR gene mutation status (if known).

7.6.2 Prior and Concomitant Medication Assessments

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

7.6.3 Efficacy Evaluations

Target and non-target lesions will be evaluated for evidence of radiographic response based on RECIST v1.1 criteria.

Tumor assessments will be performed during screening (baseline), at the end of every 8 calendar weeks (±7 days) relative to the first dose of rucaparib (Cycle 1 Day 1) up to 18 months, then every 12 calendar weeks (±7 days), until confirmed radiologic disease progression by RECIST v1.1 criteria as assessed by the investigator, loss to follow-up, withdrawal from study, death, or study closure. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than radiologically confirmed disease progression and it has been ≥ 8 weeks since the last assessment. If treatment was discontinued for reasons other than radiologic disease progression or death, radiologic tumor assessment (using the same methodology as was used at initial study screening) will continue until confirmed radiographic disease progression by RECIST v1.1 per investigator, death, loss to follow-up, withdrawal from the study, study closure, or initiation of subsequent treatment.

Tumor assessments should consist of clinical examination and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1); other studies (magnetic resonance imaging (MRI), X-ray, positron emission tomography [PET]/CT, and ultrasound) may also be performed if required. MRI may be used in place of CT scans for assessment of target lesions if required by local authorities. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. All sites of disease should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time.

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

Copies of CT scans (and other imaging, as appropriate) will be collected from all patients. IRR may be conducted on all or a subset of CT scans.

7.6.4 Safety Evaluations

7.6.4.1 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, SAEs which are related to protocol-mandated assessments will be reported. Once enrolled and rucaparib is administered, patients will be monitored for all AEs/SAEs/AESIs during study participation and until 28 days after the last dose of rucaparib. After the 28-day window, only treatment-related SAEs and all AESIs, irrespective of causality, need to be reported. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization or until loss to follow-up. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03 or later) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 8.

7.6.4.2 Clinical Laboratory Investigations

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

Hematology: red blood cell (RBC) count and parameters (hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]) and reticulocyte count, white blood cell (WBC) count and differential (with ANC), and platelet count will be assessed at screening, during treatment at each study visit, at the End of Treatment Visit, and 28-day Follow-up Visit for all patients. Hematology results must be reviewed by the investigator before the start of treatment with rucaparib and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.

Serum Chemistry: total protein, albumin, CrCL or eGFR using the Cockcroft-Gault formula or institutional standard formula, blood urea nitrogen (BUN) or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), glucose, sodium, potassium, chloride, carbon dioxide (CO_2), calcium, phosphorus, and total cholesterol, at screening, during treatment at each study visit, at the End of Treatment Visit, and 28-day Follow-up Visit for all patients. Fasting is not required before blood sampling. Serum chemistry results must be reviewed by the investigator before the start of treatment with rucaparib and ongoing at times testing occurs. Additional and more frequent tests may be performed at the investigator's discretion.

Urinalysis: performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening, during treatment at each study visit, at the End of Treatment Visit, and 28-day Follow-up Visit for all patients, but may be conducted at other times as clinically indicated.

Serum Pregnancy: for women of childbearing potential only. A serum pregnancy test must be performed ≤ 3 days prior to first dose of rucaparib (a negative result is required before dosing can begin) and at the End of Treatment Visit. A serum pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase. A positive serum pregnancy test during study participation must be reported to the sponsor. Refer to Section 8.6 for details.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results will be documented on the eCRF as an AE. Refer to Section 8.5 for guidelines on reporting of abnormal laboratory values as AEs.

7.6.4.3 Vital Signs

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

7.6.4.4 12-Lead Electrocardiogram

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

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

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

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

7.6.4.5 Body Weight and Height

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

7.6.4.6 Physical Examinations

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

7.6.4.7 ECOG Performance Status

ECOG performance status (Appendix 2) will be assessed during screening, at study visits during the Treatment Phase, at the End of Treatment Visit, and at the 28-day Follow-up Visit.

The ECOG performance status should be assessed by the same study personnel at each visit, if possible. For eligibility purposes, patients with borderline ECOG performance status should be considered carefully to avoid enrolling patients who may have significant impairment.

7.6.5 Biomarker Analysis – Tumor Tissue

7.6.5.1 Biomarker Analysis – Mandatory Tumor Tissue Collection

Submission of pre-treatment tumor tissue is mandatory, and defined as a biopsy or surgical specimen obtained prior to the first dose of rucaparib from a primary or metastatic soft tissue tumor lesion that has not been previously irradiated. Ascites is not an acceptable specimen for the tumor tissue requirement. If tumor tissue was collected within 6 months of the first dose of rucaparib and no intervening anti-cancer treatments were administered during this period, this tissue may be submitted for the pre-treatment tumor tissue requirement. The tumor tissue should be of adequate quality for molecular profiling and be provided in the form of an FFPE block or unstained slides (see Pathology Charter). The required pre-treatment tumor tissue should be submitted to the sponsor's laboratory by Cycle 2 Day 1 of study treatment, and an associated pathology report should accompany each tumor sample specimen.

The submitted tumor samples will undergo central HRD testing in order to assess each participant's HRD tumor status by NGS molecular profiling. 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 detected from this testing, the finding will be made available to the investigator provided the results are generated from a CLIA-certified laboratory and the patient has consented to receive the results.

Additional genomic, transcriptional, or epigenetics assays may also be performed on available specimens to understand the genomics of bladder cancer, as well as molecular factors driving the response and resistance to rucaparib.

7.6.5.2 Biomarker Analysis –Archival Biopsy

Archival FFPE tumor tissue must be submitted if available. There is no age limit to these samples. If available, a pathology report should be included with the specimen. Sample details will be provided in the Pathology Charter.

These samples will be used for molecular profiling to understand the genomics of bladder cancer, as well as the evolution and impact of intervening therapies on molecular drivers of rucaparib sensitivity.

7.6.5.3 Biomarker Analysis – Optional Biopsy after progression

End of treatment and/or upon progression tumor biopsies are not mandatory, but their collection is strongly encouraged, and will be used for molecular profiling to determine potential mechanisms of resistance to rucaparib. Patients must provide additional consent for the optional tumor tissue biopsy sample. New lesions or lesions that are growing should be

prioritized for the optional biopsy. If possible, collect the lesion responsible for progression. Sample collection details will be provided in the Pathology Charter.

7.6.6 Biomarker Analysis – ctDNA from Blood

Blood samples for plasma ctDNA will be collected during screening, before dosing on Day 1 of Cycles 1, 2, 3, and at every 8 weeks thereafter coinciding with radiographic scans, and at the end of treatment discontinuation from all patients entered in the study. Sample collection details will be provided in the Laboratory Manual.

These samples will be used for ctDNA profiling to assess alterations in genes that may be associated with response and resistance to rucaparib.

7.6.7 Biomarker Analysis - Genomic DNA from Blood

A blood sample for genomic analysis will be collected at Cycle 1 Day 1 from all patients. Sample collection details will be provided in the Laboratory Manual.

Genomic DNA may be purified and tested to determine whether any mutations identified from NGS tissue testing are of germline origin. Because the germline analysis will be done near the end of the study, there are no plans to share these results with the investigator and the patient. 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 detected, these incidental finding will be made available to the investigator provided the results are generated from a CLIA-certified laboratory and the patient has consented to receive the results.

7.6.8 Pharmacokinetics Evaluation

Plasma samples are to be collected for trough level PK analysis of rucaparib 1 hour before the morning dose on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1. If the start of the next dose is postponed or suspended, the PK sample should be collected as close as possible to 12 hours after the previous dose. Refer to the Laboratory Manual for sample collection details for PK samples.

8 ADVERSE EVENT MANAGEMENT

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 under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening, are not considered AEs.

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

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 rucaparib through 28 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing, that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity
- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 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

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

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor within 24 hours (see Section 8.9 for reporting 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 rucaparib or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page.
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE/SAE.
- Events that meet the SAE criteria (as outlined in Section 8.2) and occur after informed consent, but before the first dose of rucaparib, which are considered unrelated to 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 lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any 1 of the following criteria is met:

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

8.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the course of the study, rucaparib dosing should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies occurring during study participation or within 6 months of last dosing must be reported to the sponsor using the Pregnancy Report Form within the same timelines as for an SAE.

All pregnancies should be followed through to outcome. Once the outcome of a pregnancy is known, the Pregnancy Outcome Report Form should be completed and submitted 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 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Events that occur after signing of informed consent, but prior to initiation of rucaparib, unless due to a protocol-mandated procedure, will be recorded on the Medical History eCRF. Any event related to a protocol-mandated procedure should be reported during the screening period. Any AE that occurs after first dose of rucaparib through 28 days after receiving the last dose of rucaparib will be recorded on the AE eCRF. After the 28-day reporting window after discontinuation of rucaparib treatment, only SAEs assessed as related to rucaparib and all AESIs, irrespective of causality, need to be reported. 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,** severity, and seriousness to the investigational drug. The action taken and the outcome must also be recorded.

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

8.7.1 Onset Date of Adverse Events

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

8.7.2 Resolution Date of Adverse Events

The resolution date is the date that the events or the signs/symptoms related to the event resolved or resolved with sequelae or enter the resolution date as the date when the patient has reached a new baseline if 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, Version 4.03 or later grading scale (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).[43]

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
- Fatal events are those events that led to the patient's death

8.7.4 Causal Relationship of Adverse Events to Rucaparib

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

Table 6. Causal Relationship of Adverse Events to Rucaparib

Causality	Description
Not Related to Rucaparib	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of rucaparib • It does not follow a known pattern of response to rucaparib • It does not reappear or worsen when rucaparib is restarted • An alternative explanation is likely, but not clearly identifiable

Table 6. Causal Relationship of Adverse Events to Rucaparib

Causality	Description
Related to Rucaparib	• An AE that is difficult to assign to alternative causes • It follows a strong or reasonable temporal sequence from administration of rucaparib • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient • It follows a known response pattern to rucaparib • It is confirmed with a positive re-challenge 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 rucaparib. 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, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

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

All SAEs and AESIs, regardless of relationship to rucaparib, must be reported to the sponsor/ SAE designee **within 24 hours** of knowledge of the event, during the study through 28 days after receiving the last dose of study treatment, according to the procedures below. After the 28-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. 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. The Serious Adverse Event (SAE)/ Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/ AESI Reporting Form and Pregnancy Report Forms.

The 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; to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

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

The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the 25th, 50th (median), and 75th percentiles with the 95% confidence interval (CI) will be summarized. The number of patients with events and the number of censored patients will also be presented.

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 rucaparib administration.

All statistical analyses will be conducted with the SAS® System, Version 9.3 or higher. Further details regarding the statistical analyses planned in this study will be outlined in the SAP.

9.2 Analysis Populations

The following analysis populations are defined for the study:

Safety Population – The safety population will include all patients who received at least 1 dose of rucaparib.

Intent-to-treat Population (ITT) – The ITT population will include all patients who received at least 1 dose of rucaparib.

HRD-positive Population – Tumor tissue will be analyzed to determine the percentage of genomic LOH,[31] and patients will be classified as HRD-positive or HRD-negative based on a prespecified LOH cut-off defined in the SAP. The HRD-positive population will include all patients who received at least 1 dose of rucaparib and are classified as HRD-positive.

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

Demographic (eg, age, race, and ethnicity as allowed by local regulations) and key baseline characteristics will be summarized for the safety and ITT populations.

9.5 Efficacy Analyses

All efficacy analyses will be conducted using the ITT and HRD-positive populations.

9.5.1 Primary Efficacy Analyses

The primary efficacy endpoint of ORR is defined as a best confirmed response of CR or PR by RECIST v1.1 (Appendix 1) as assessed by the investigator. The ORR will be summarized with frequencies and percentages for the ITT and HRD-positive populations as well as other HRD subgroups.

9.5.2 Secondary Efficacy Analyses

9.5.2.1 Duration of Response

Duration of confirmed response is defined as the time from the date that a response is first reported to the time that progression is first documented after the confirmed response.

9.5.2.2 Progression-free Survival

Progression-free survival (PFS) will be calculated as 1+ the number of days from the first dose of rucaparib to disease progression or death due to any cause, whichever occurs first. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (ie, radiologic assessment) or date of first dose of rucaparib if no post-baseline tumor assessments have been performed.

9.5.2.3 Overall Survival

Overall survival (OS) is defined as the date from first dose of rucaparib to the date of death due to any cause. Patients who have not died will be censored at the date last known to be alive.

9.5.3 Exploratory Efficacy Analyses

9.5.3.1 Evaluation of Biomarkers of Response to Rucaparib

Next-generation sequencing (NGS) will be performed to measure defects in HRR genes and determine their correlation with response. Genomic alterations that may be assessed include deleterious mono- and bi- allelic variants in genes of the HRR pathway, genome-wide LOH, telomeric allelic imbalance (TAI), large-scale state transitions (LST), and tumor mutational burden. Patients will be classified based on the presence or absence of these markers of HRD, and possible associations of these biomarkers with response to rucaparib will be explored.

9.5.3.2 Evaluation of Circulating Tumor DNA as a Molecular Marker of Response

Pairwise comparisons will be performed for HRR genotyping results between centrally-assessed screening biopsy tissue, archival primary tissue (where available), and plasma ctDNA in all combinations. In particular, the concordance of genotyping results between

archival primary tissue and screening biopsy tissue will be assessed to explore whether the HRD status of the archival primary specimen accurately reflects that found in a screening tissue biopsy. Additionally, the sensitivity and specificity of plasma HRD assessment relative to the tissue results will be explored.

9.6 Pharmacokinetic Analyses

In all patients with at least 1 PK sample collected, the trough plasma rucaparib PK data (C_{min}) and summary statistics (N, mean, StD, minimum, median, maximum, coefficient of variation [CV]%]) will be reported.

9.6.1 Exploratory Population Pharmacokinetics and Exposure-Response Analyses

The PK data and selected safety and efficacy endpoints will be included in exploratory population PK and exposure-response analyses, and the results will be reported separately.

9.7 Safety Analyses

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

Data from all patients in the safety population will be included in the safety analyses. AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

9.7.1 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 Version 4.03 or later. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of rucaparib until the date of the last rucaparib dose plus 28 days.

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 1 TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or higher TEAEs;
- Treatment-related TEAEs;
- Serious TEAEs;

- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication;
- TEAEs resulting in interruption/delay of study medication; and
- TEAEs resulting in dose reduction of study medication.

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

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

9.7.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will generally be presented in International System of Units (SI) units. The on-treatment period will be defined as the time from the first dose of rucaparib to 28 days after the last dose of rucaparib. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

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

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

9.7.3 Vital Sign Measurements

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

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

9.8 Exploratory Biomarker Analysis

9.8.1 Evaluation of Changes in Tumor Samples and Changes in Circulating Cell-free Tumor DNA

Molecular profiling of ctDNA will be performed to assess changes over time that may be associated with response and resistance to rucaparib. The analysis will include, but not be limited to, allele frequencies and emergence of HRR gene mutations and alterations in other components of DNA repair and oncogenic signaling pathways.

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

9.8.2 Evaluation of Biomarkers of Resistance to Rucaparib

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

9.9 Sample Size Considerations

The overall sample size was determined by considering the number of patients needed for adequate safety and activity assessment of HRD-positive patients. Based on the estimated prevalence of 60% HRD-positive patients in this population, approximately 200 patients will be enrolled into the study. This would result in enrollment of approximately 120 HRD-positive patients. The overall sample size will enable robust estimates of response for the ITT population as well as allow for an exploration to define the optimal HRD signature that correlates with response to rucaparib. The null hypothesis for response rate based on historical data in similar patient populations is p=0.10. With a total sample size of 200 patients, the study has greater than 90% power to reject the null hypothesis at a 5% significance level if the true response rate for rucaparib is 20%.

9.10 Interim Analysis

A group sequential interim monitoring plan will be implemented in order to help guide the DMC in monitoring the study. The null hypothesis is p=0.10 based on historical data in similar patient populations. The study has greater than 90% power to reject the null hypothesis at a 5% significance level if the true response rate for rucaparib is 20%.

Interim analyses will be performed when approximately 60 patients and 120 patients have complete data, defined as a documented response (PR or CR), disease progression, or at least 4 months of disease assessment data available.

If the response rate does not meet continuance criteria for the ITT population, the DMC will further evaluate the benefit: risk for study treatment, both overall and separately for patients in different HRD subgroups, and make a recommendation whether further enrollment into 1 or all groups should be discontinued.

Additional details regarding this group sequential interim monitoring plan are provided in Appendix 4.

10 PATIENT DISPOSITION

10.1 Removal of Patients from the Study or Study Drug

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

- Consent withdrawal for any reason at the patient's own request or at the request of their legally authorized representative (where acceptable according to national law and/or local regulations);
- Radiographic progression of patient's underlying cancer per RECIST v1.1 (unless, in the opinion of the investigator, the patient continues to derive clinical benefit; treatment beyond progression is permitted with additional consent);
- Unequivocal clinical progression of the patient's underlying cancer that, in the opinion of the investigator, requires immediate change in systemic anti-cancer therapy, or results in marked deterioration in ECOG performance status to Grade 3 or higher
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy; or
- Noncompliance by the patient with protocol mandated procedures.

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

The sponsor may discontinue the study early for any of the reasons noted in Section 11.7.

11 STUDY ADMINISTRATION

11.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; ICH E6 (R2); FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki. The ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CRF50) and applicable local requirements.

11.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent) and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

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. The trial will be registered on www.clinicaltrials.gov, EudraCT, and other applicable trial registry systems as appropriate.

11.1.2 Institutional Review Board or Independent Ethics Committee Approval

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/IRB. 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 IEC/IRB. The principal investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IEC/IRB with all appropriate materials.

Verification of the IEC's/ IRB's unconditional approval of the study protocol and the written Informed Consent Form (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.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the investigator has obtained the signed and dated ICF, and the sponsor is notified.

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

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

11.2 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 Good Clinical Practice (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 IEC/ IRB 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 IEC/ IRB. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/ or relatives, guardians, or legal representatives, 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 explaining the study and with whom the patient can discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original ICF will be filed in the investigator file unless otherwise agreed.

The patient will have the option to provide additional consent to allow or not allow the sponsor to retain residual samples for future unspecified research.

11.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient identifiers such as year of birth, and an identification code (ie, not names) should be recorded on any form submitted to the sponsor and the IRB/ IEC. The investigator must record all screened and enrolled patients. Enrolled patients will be recorded in the eCRF. The investigator must maintain a list with the identity of all treated patients, but not intended for use by the sponsor.

The investigator agrees that all information received from the sponsor or designee including, but not limited to, the Investigator's Brochure (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 by any employee or agent of the study center to any third party or otherwise into the public domain.

11.4 Study Monitoring

On behalf of the sponsor, a contract research organization (CRO) or contract monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless the sponsor or the CRO has worked with the center recently, in which case this initial visit may be waived) and at appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit. Visits may also be conducted by sponsor personnel.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (ie, the various study records, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification and review). 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.

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.

11.5 Case Report Forms and Study Data

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events [AEs], concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Medidata RAVE, a 21 CFR Part 11-compliant data capture 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. Clinical data will be entered directly from the source documents.

11.6 Data Monitoring Committee

A DMC will be established to review safety data in compliance with a prospective charter. The DMC will comprise coordinating investigators and sponsor representatives. The DMC responsibilities, authorities, and procedures for this study will be documented in the DMC Charter, which will be endorsed by the DMC members and signed by the DMC chair prior to the first data review meeting. The DMC will also ensure the study is beneficial to patients (see Section 9.10).

The DMC will meet after the first 20 patients received rucaparib for at least 28 days or discontinued study treatment, and then approximately every 6 months after sufficient data have been collected. Safety and efficacy will be assessed by the DMC at the interim analyses at 60 and 120 patients. The DMC chairperson or sponsor may convene an unscheduled DMC meeting if there are newly identified significant safety concerns. Following data review, the DMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup. Details regarding the DMC will be in the committee charter.

11.7 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

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

The sponsor reserves the right to 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 rucaparib.

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

11.8 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/ IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

11.9 Retention of Data

The study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and the sponsor, and other study-related documents. The investigator should have control of all essential documents generated by the site. Source documents must be maintained, ALCOAC (attributable, legible, contemporaneous/complete, original, accurate) used. Any changes to source data should be traceable.

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 should have control of and continuous access to the eCRF data.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data 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 trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

11.10 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) that take a risk-based approach to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

11.10.1 Changes to the Protocol and Deviations

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

If changes to the study are required, they must be provided in a formal protocol amendment having been approved by an appropriate IRB/IEC.

11.10.2 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 the design, conduct, procedures, and administrative aspects of this study. This may include, but is not limited to, onsite 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.

In accordance with Code of Federal Regulations 21 CFR 312.56, ICH GCP and local regulations, the clinical monitor will periodically inspect eCRFs, study documents, medical records (office, clinic, or hospital) for patients in this study (anonymity is to be preserved), research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after 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.

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

The 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 or other regulatory agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the sponsor immediately. The investigator will ensure that the auditors 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.

11.11 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the sponsor and signed by the sponsor's chief medical officer, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

11.12 Publication and Disclosure Policy

All data generated from this study are the property of the sponsor and shall be held in strict confidence along with all information furnished by the sponsor. 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. Written permission to the investigator will be contingent on the review by the sponsor of the statistical analysis and manuscript, and will provide for nondisclosure of the sponsor's 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.

11.13 Investigator Oversight

The investigator has a responsibility for supervising all delegated staff. All staff delegated study responsibilities must be documented on an approved Delegation of Authority log for the study and this filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by training, experience, and licensure (as applicable). The investigator should implement procedures to ensure integrity of the study and data generated.

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13 APPENDICES

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Appendix 1 Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[44] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with the following:

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

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

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

Nonmeasurable Disease:

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

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

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

Nontarget Lesions

RECIST 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

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 partial response 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 lesions is also considered progression.

Abbreviations: LD = longest diameter; PD = 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 lesions and/or unequivocal progression of existing nontarget lesions.

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

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not 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

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

Patients with a 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 the 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.

Confirmatory Measurement/Duration of Response

Confirmation

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

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).

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

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.

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

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

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

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

Appendix 3 Examples of Sensitive Clinical Cytochrome P450 (CYP) Substrates

CYP Enzyme	Sensitive Substrates[a]
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine
CYP2C9	celecoxib
CYP2C19	S-mephenytoin, omeprazole
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

[a] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

Source: Draft FDA Guidance on Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications, 2017.[45] More example drugs can be found at the FDA's website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

Appendix 4 Group Sequential Interim Monitoring Plan

Introduction

This plan describes an adaptive study design for the evaluation of rucaparib in patients with locally advanced or metastatic urothelial carcinoma. The adaptive design utilizes interim analyses that allow for early stopping for futility after DMC review of futility analysis of the ITT population, the efficacy for HRD subgroups and all safety analyses.

The trial will enroll 60-200 subjects in a single experimental arm.

Objective response rate by RECIST v1.1 as assessed by the investigator will be summarized for the ITT and HRD-positive populations as well as for the exploratory HRD groups.

Primary Analysis

Let p be the true response rate. The primary analysis compares p to a performance goal of 0.10, and is thus a hypothesis test of

$$H_0 : p \leq 0.10 \qquad H_1 : p > 0.10$$

Starting with a noninformative Beta(0.1,0.9) prior on p, the posterior distribution is

$$p|data \sim Beta(0.1+Y, 0.9+N-Y)$$

where Y is the observed number of responses and N is the number of complete subjects in the trial. The trial is a success if

$$Pr(p > 0.10 \mid data) > 0.95$$

This threshold maintains type I error at 5%. We consider an alternative threshold (0.935) that increases type I error slightly but obtains greater power for comparison.

Design

The trial sequentially enrolls patients and interim analyses are conducted. At the time of each interim analysis, there will be N patients with a 4-month endpoint and M patients that are incomplete. Let Y be the number of responders among the complete patients.

The model computes p_{max}, the predictive probability of trial success if the trial is followed to the maximum (targeted) sample size and all patients are followed to completion. Let W_{max} be the number of eventual responders among the unknown patients (incomplete and currently unenrolled). The distribution of W_{max} is a BetaBinomial(MAXN-N,0.1+Y,0.9+N-Y). The predictive probability p_{max} is the probability W_{max} results in trial success when N=200 subjects are complete.

The model indicates trial futility at any interim analysis if p_{max}<threshold, indicating that there is limited probability that the trial will reach success even at the maximum sample size.

For this study design with N=60 minimum, N=200 maximum, a 5% futility threshold, and interims at N=60 and N=120, the required number of successes to continue is summarized in the table below. For example, in the first row we require 5/60, indicating we must have at least 5 successes out of the first 60 patients (so 5 would continue).

Interim	Minimum to Continue (5% predictive probability)
1 (N=60)	5/60 (8.3%)
2 (N=120)	13/120 (10.8%)

Example Trials

Example trial 1

The trial enrolls until the first interim analysis at N=60 ITT patients complete. At this interim, we have 13/60 (21.7%) responses with 40 patients awaiting follow-up. This result is clearly encouraging compared to a 10% baseline rate. With 140 patients still requiring data, the predictive probability of success on the ITT population is 97.5%, well above the threshold for futility. Response among HRD subgroups is evaluated and the trial continues.

The second interim analysis occurs with N=120 ITT patients complete, obtaining 22/120 (18.3%) with 27 incomplete. Response among HRD subgroups is evaluated. With 80 patients remaining needing follow-up, the predictive probability of success is 99.0%, clearly high and the trial continues.

At N=200, we obtain 37/163 responses (22.7%). This results in a posterior probability greater than 99.99% and a successful trial.

Example Trial 2

The trial enrolls until the first interim analysis at N=60 ITT patients complete. At this interim, we have 3/60 (5%) responses with 40 patients awaiting follow-up. The predictive probability of success at this point is only 0.4%. This is below the threshold for futility for the ITT population. The DMC would examine response among HRD subgroups as well as safety data and make a recommendation to stop the trial or continue. If the trial was stopped at this point, it is assumed that all enrolled patients will continue to be followed.

In that follow-up, the trial ended with 12/100 responses (12%). While greater than 10%, this is insufficient for a successful trial (Pr(trmt beats ctrl)=56.7%) and the trial would have been very unlikely to meet its primary objective even had N=200 subjects been enrolled.

Example Trial 3

The trial enrolls until the first interim analysis at N=60 ITT patients complete. At this interim, we have 5/60 (8.3%) responses with 40 patients awaiting follow-up. With 140 patients still requiring data, the predictive probability of success on ITT is 5.1%, barely

above the threshold for futility. Response among HRD subgroups is evaluated and the trial continues.

The second interim analysis occurs with N=120 complete, obtaining 14/120 (11.7%) with 31 incomplete. With 80 patients remaining needing follow-up, the predictive probability of success is 13.1%, also high enough to continue. Response among HRD subgroups is evaluated and the DMC recommends that the trial continue.

At N=200, we obtain 20/200 responses (10.0%). This results in a posterior probability of 47.5% and a nonsuccessful trial.

Simulations and Operating Characteristics

The operating characteristics of this trial were determined through trial simulation and compared to a potential Simon 2-stage design. We computed the operating characteristics under the assumptions that p=0.10 (null hypothesis) and p=0.11, 0.12, …, 0.25.

A total of 10,000 trials were simulated per scenario. In each, subjects were accrued according to a Poisson process with an average of 1.5 subjects per week. In each simulated trial, interims analyses were conducted according to prespecified rules and the results were recorded.

The detailed results are shown in the following tables for Expected Sample size and for Power, respectively.

Expected Sample Size	p=0.10 (null)	p=0.15	p=0.20	p=0.25
Fixed	200.00	200.00	200.00	200.00
Simon	141.52	188.83	204.28	205.92
Adjusted	**150.85**	**192.38**	**199.60**	**199.98**
Unadjusted	151.60	192.67	199.40	199.99

Pr(trial success)	p=0.10 (null)	p=0.15	p=0.20	p=0.25
Fixed	0.043	0.683	0.989	0.999
Simon	0.049	0.673	0.977	0.999
Adjusted	**0.062**	**0.736**	**0.991**	**1.000**
Unadjusted	0.039	0.675	0.985	0.999

The next table shows the details of if and where each of the adjusted adaptive trial simulations stopped for futility. For each simulated trial, the trial could stop at N=60 complete, N=120, or run to the maximum sample size. Note that trials that stop at N=60 or N=120 complete actually we enroll more than 60 or 120 subjects due to the "overrun," patients enrolled while waiting for the required patient to complete. In addition, we summarize the probability of a "futility to success flip flop" (FSFF). In actual

implementation, when a trial is stopped for futility, you will not get to see what would have happened had you enrolled until N=200. However, in simulation we can simulate those remaining subjects and determine how many futility stops occurred for trials that would ultimately have been successful.

Pr(trial success)	p=0.10 (null)	p=0.15	p=0.20	p=0.25
Futility N=60	0.270	0.042	0.004	0.000
Futility N=120	0.331	0.054	0.000	0.000
Pr(FSFF)	0.004	0.022	0.004	0.000