A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with *gBRCA* Mutation Ovarian Cancer or Other Solid Tumor

Protocol Number:	CO-338-010
Investigational Product:	Oral rucaparib (CO-338)
Eudra CT Number:	[redacted]
IND Number:	[redacted]
Development Phase:	Phase I/II
Indication Studied:	Locally advanced or metastatic solid tumors, including lymphoma, and germline *BRCA* (*gBRCA*) ovarian cancer
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway, Suite 100 Boulder, CO 80301 U.S.A.
	[redacted]
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. Essential study documents will be archived in accordance with applicable regulations.

[redacted]

[redacted]

CONFIDENTIALITY STATEMENT

Protocol Approval Signature Page

Protocol: CO-338-010
Title: A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with *gBRCA* Mutation Ovarian Cancer, or Other Solid Tumor

[redacted]

Protocol Acceptance Form

Protocol: CO-338-010

Title: A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with *gBRCA* Mutation Ovarian Cancer, or Other Solid Tumor

Date: 29 June 2016

[redacted] [redacted]

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

Investigator's Signature | Date

Name (printed)

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1 SYNOPSIS

Protocol Number	CO-338-010
Title	A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with *gBRCA* Mutation Ovarian Cancer or Other Solid Tumor
Phase	Phase I/II
Introduction and Study Overview	Rucaparib (CO-338; formerly known as PF 01367338 and AG 14699) is a small molecule inhibitor of poly-adenosine diphosphate [ADP] ribose polymerase (PARP) being developed for antitumor therapy; an oral formulation as monotherapy is the focus of current development efforts. Rucaparib is currently being investigated as monotherapy in patients with cancer associated with breast cancer 1 or 2 gene (*BRCA1* or *BRCA2*) mutations, or other alterations or evidence of homologous recombination deficiency (HRD). The purpose of Part 1 of this study is to initially determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) of oral rucaparib administered on a continuous daily basis to patients with solid tumors, inclusive of lymphoma, who have progressed on prior treatment. Once provisionally established, the RP2D will be evaluated in an expanded cohort of patients with a solid tumor and evidence of a deleterious germline mutation of *BRCA1 or BRCA2 (gBRCA)*. Once confirmed to be the optimal dose, the RP2D will be administered in the Phase II portion to patients with: • Part 2A: Platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer with evidence of a *gBRCA* mutation who have received at least two, but no more than four, prior regimens • Part 2B: Relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with evidence of a deleterious *BRCA* mutation (germline or somatic) who have received at least three, but no more than four, prior chemotherapy regimens • Part 3: Any advanced solid tumor, inclusive of lymphoma, with evidence of a *BRCA* mutation (germline or somatic); prior PARP inhibitor treatment is allowed provided it was not the last treatment received and/or treatment was not received within the last 6 months It is anticipated that rucaparib will promote cell death in the BRCA-deficient tumor cells of these patients, thereby limiting tumor progression and providing therapeutic benefit. The study will encompass 3 parts: • Part 1 (Phase I portion) = Six to twelve estimated dose-escalation cohorts in patients with solid tumors and RP2D Expansion in patients with a solid tumor and evidence of a deleterious *gBRCA* mutation • Part 2 (Phase II portion) = Evaluation of the RP2D in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a known deleterious *BRCA* mutation (germline or somatic)

<table>
<tr><td>Introduction and Study Overview (cont)</td><td colspan="2">• Part 3 (Phase II PK portion) = Further evaluation of PK of higher dose strength tablets at the RP2D in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation (germline or somatic)</td></tr>
<tr><td>Planned Number of Patients</td><td colspan="2">Number of patients:
• Part 1: approximately 50 – 60 patients
• Part 2: up to 41 evaluable patients in Part 2A and 40 evaluable patients in Part 2B
• Part 3: approximately 20 evaluable patients
Patients will enroll in to either Part 1, Part 2, or Part 3 of the study, not in to multiple parts.</td></tr>
<tr><td>Planned Number of Sites</td><td colspan="2">This is a multicenter, multinational study. Patients will be enrolled from approximately 4 – 6 sites in Part 1, approximately 20 sites in Part 2, and approximately 8 sites in Part 3.</td></tr>
<tr><td rowspan="4">Study Objectives and Endpoints</td><td colspan="2">Primary, secondary, and exploratory objectives and endpoints are shown below.</td></tr>
<tr><td>Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td>To evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumors, and to determine the MTD and RP2D (Part 1 only)</td><td>The incidence of Grade 3 or 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)</td></tr>
<tr><td>To characterize the pharmacokinetic (PK) profile of oral rucaparib when administered as a continuous daily dose (Part 1 and Part 3 only)</td><td>PK parameters: area under the curve from time zero to the time with the last measurable concentration (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (k_{el}), apparent volume of distribution at steady state after nonintravenous administration (V_{ss}/F), and apparent total plasma clearance (Cl/F)</td></tr>
<tr><td>To evaluate overall response rate (ORR) in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a BRCA mutation (Part 2 only) [henceforth abbreviated to ovarian cancer (OC) population]</td><td>ORR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1; secondary analysis including Gynecologic Cancer InterGroup (GCIG) cancer antigen-125 (CA-125) criteria</td></tr>
</table>

Study Objectives and Endpoints (cont)	**Secondary Objectives**	**Secondary Endpoints**
	To characterize the single-dose PK profile of oral rucaparib after a high-fat breakfast compared to that in the fasted state ***(Part 1 and Part 3 only)***	PK parameters C_{max} and AUC (fasted and fed)
	To evaluate the effects of oral rucaparib on the QT/QTc interval measured by electrocardiogram (ECG) ***(Part 1 only)***	Change from baseline in QT/QTc interval
	To evaluate the safety and tolerability of oral rucaparib ***(Parts 1, 2, and 3)***	The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
	To evaluate antitumor activity of oral rucaparib in various solid tumors ***(Part 1 and Part 3 only)***	Response per RECIST v1.1; additional analyses including applicable tumor markers
	To assess progression-free survival (PFS) in the OC population ***(Part 2 only)***	PFS defined as the time to first occurrence of disease progression per RECIST v1.1 or death
	To evaluate duration of response in the OC population ***(Part 2 only)***	Duration of response per RECIST v1.1.
	To evaluate survival ***(Part 2B only)***	Overall survival (OS)
	Exploratory Objectives	**Exploratory Endpoints**
	To explore the relationship between the PK of oral rucaparib and the potential changes in QT/QTc interval ***(Part 1 only)***	QT/QTc interval correlated with plasma concentrations of oral rucaparib
	To profile circulating metabolites of oral rucaparib at steady state at the RP2D ***(Part 1 only)***	Metabolic profile in the Day 15 plasma samples
	To explore the association between genomic alterations identified in tumor tissue and clinical outcome (Parts 1, 2, and 3)	Mutational status of *BRCA1/2* and other homologous recombination genes. Genomic scarring/ loss of heterozygosity (LOH) assessment in tumor tissue. Response by RECIST v1.1 and/or tumor markers (i.e., CA-125)

Study Design	All patients will undergo screening assessments within 30 days prior to the first dose of oral rucaparib. Study-procedure-related AEs that occur after signing of the informed consent form and before administration of oral rucaparib will also be collected during this period. **Part 1 (Phase I Portion)** In Part 1, there will be an estimated six to twelve dose-escalation cohorts, with a minimum of three patients enrolled in each cohort, and an expanded evaluation of the RP2D in up to 15 patients. Treatment cycles will comprise 21 days of continuous dosing. All dose escalations will be based on assessment of DLTs, overall safety and tolerability, and PK that occur with each cohort, and will be agreed upon between the investigators and sponsor. The MTD is defined as the maximum daily oral dose at which <33% of patients experience a DLT during Cycle 1 (Safety and PK Assessment Period). If a DLT is observed in one of three patients, then three additional patients will be enrolled at that same dose level. Dose escalation will continue until at least two of the three to six patients treated at a dose level experience a DLT. The next lower dose will then be considered the MTD. Alternatively, if the dose between the MTD and the maximally delivered dose is significant (such as 100%), then a more modestly de-escalated dose may be explored (e.g., 20–50%). <u>RP2D Selection and Expansion</u> The RP2D for evaluation in Part 2 will be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data. The RP2D may or may not be the same as the MTD identified in Part 1. For example, if the MTD is not reached, or if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RP2D may be a different, though not higher, dose than the MTD. Once the RP2D has been provisionally established, up to 15 additional patients with a solid tumor and evidence of a deleterious *gBRCA* mutation will be enrolled and treated at that dose in order to further characterize safety, tolerability, and PK and confirm that this is the optimal dose to evaluate in Part 2 (Phase II portion). Since the RP2D may be selected based on evaluation of as few as 3 patients, there is low certainty that the RP2D has a DLT rate that is <33%.[1] Enrolling up to an additional 15 patients will increase the certainty that the Phase II component of the study is evaluated at a dose with a DLT rate <33%. If ≥33% of patients at the RP2D experience a DLT, then enrollment into the RP2D Expansion cohort will stop and an alternative dose will be explored. <u>Food-Effect PK Evaluation</u> The effect of food on oral rucaparib PK will be assessed prior to, and during, Cycle 1 in three patients. Food effect PK analysis will be performed once evaluation of Cohort 1 (40 mg) is completed, and will be conducted either at the next escalated dose or as expanded PK evaluation of the 40 mg dose level. The dose level for evaluation will be established at the safety teleconference call for Cohort 1. Food-effect PK may be conducted in additional cohorts in Part 1, if results from prior cohort(s) warrant expanded evaluation.

Study Design (cont)	Effect on QTc ECGs will be collected in all patients enrolled in Part 1, including those in the RP2D Expansion cohort, in order to assess the effect of rucaparib on QTc. ECGs in Part 1 will be performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory. Local ECG monitoring may be conducted once a sufficient amount of data has been reviewed by the core/central laboratory. Metabolic Profiling The first three patients enrolled into the RP2D Expansion cohort will have additional blood samples collected on Day 1 (predose sample only) and Day 15 of Cycle 1 for assessment of plasma metabolites. Treatment-Extension Period Upon completion of Cycle 1 (Safety and PK Assessment Period), Part 1 patients may participate in an optional Treatment-Extension Period, which begins on Day 1 of Cycle 2. Oral rucaparib will be administered daily during this period (21 day cycles) until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study. **Part 2 (Phase II Portion in *BRCA*-Mutant Ovarian Cancer)** Enrollment into Part 2 will begin when all patients enrolled into the RP2D Expansion cohort have completed 2 cycles of treatment, or have discontinued from the study prior to completing 2 cycles. Patients in Part 2 will be assessed for tolerability and efficacy. Patients will be treated until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study. The study will use a Simon 2-stage design to evaluate the efficacy of rucaparib in Part 2 (Phase II portion). Initially, 21 patients will be treated in Stage 1; if two or more patients in Stage 1 have an objective response (complete response [CR] or partial response [PR]) then the remaining 20 patients will be treated in Stage 2. If fewer than two patients in Stage 1 have an objective response, then no further patients will be enrolled. The criteria for Stage 1 success were met in April 2014, and Stage 2 enrollment of 41 patients was completed in April 2015. An additional cohort of approximately 40 *BRCA* mutant OC patients will be evaluated in Part 2B. This portion of the study will evaluate the efficacy of rucaparib in ovarian cancer patients with a deleterious *BRCA* mutation (germline or somatic) who received ≥3 (but no more than 4) prior chemotherapy regimens. **Part 3 (Phase II PK Portion in Patients with any Advanced Solid Tumor)** Part 3 will enroll in parallel with Part 2. Patients in Part 3 will be assessed for PK, safety and tolerability, and anti-tumor activity. Patients will be treated until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study. All patients enrolled into Part 3 will have plasma samples drawn in order to evaluate the PK profile of a single 600 mg dose administered as 300 mg tablets in the fed versus fasted state. Plasma samples will also be drawn from all patients to evaluate the steady state PK profile of 600 mg BID administered as 300 mg tablets.

Study Design (cont)	**Part 1, Part 2 and Part 3--End of Treatment and Follow-up Assessments** All patients should have end of treatment assessments performed upon discontinuation of rucaparib and should return to the clinic for AE assessment at 28 (±3) days after the last dose of rucaparib has been administered. During Parts 1 to 3, AEs will be assessed from the time of informed consent through 28 days after the last dose. Part 2B patients will be followed for survival, subsequent anti-cancer treatments. and secondary malignancy monitoring every 12 weeks [±7 days].
Dose-Limiting Toxicities	DLTs in Part 1 are defined as any of the following events that occur during Cycle 1 (Safety and PK Assessment Period) and are assessed by the investigator as related to rucaparib. Where applicable, events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).[2] • Absolute neutrophil count (ANC) $<0.5 \times 10^9$/L >5 days duration or febrile neutropenia (i.e., fever >38.3°C with ANC $<1.0 \times 10^9$/L) • Platelets $<25 \times 10^9$/L or platelets $<50 \times 10^9$/L with bleeding requiring a platelet transfusion • Grade 4 anemia (i.e., life-threatening consequences; urgent intervention indicated) • Any non-hematological AE CTCAE Grade 3 or greater (except alopecia and nausea, vomiting, and diarrhea if well controlled by systemic medication) In order to be considered evaluable for dose-escalation decisions, a patient in Part 1 must have received at least 17 complete days of dosing, and have completed Cycle 1, Day 21 without a DLT, or have experienced a DLT in Cycle 1. If a patient withdraws from the study without having met either of these criteria, then an additional patient will be enrolled in that cohort.
Study Population	**Inclusion Criteria** All patients enrolling into **Part 1 (Phase I portion), Parts 2 or 3 (Phase II portions)** must meet all of the following inclusion criteria: • Understand and voluntarily sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation • Be ≥18 years of age at the time the informed consent form is signed • Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 • Have life expectancy of at least 3 months • Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of rucaparib: a. Bone Marrow Function – ANC $\geq 1.5 \times 10^9$/L – Platelets $>100 \times 10^9$/L – Hemoglobin ≥9 g/dL

Study Population (cont)	b. Hepatic Function – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN); if liver metastases, then ≤5 × ULN – Bilirubin ≤1.5 × ULN (<2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome) – Serum albumin ≥30 g/L (3.0 g/dL) ***(Part 2B only)*** c. Renal Function – Serum creatinine ≤1.5 × ULN Patients enrolling into **Part 1 (Phase I portion)** must also meet the following inclusion criteria: • Have a histologically or cytologically confirmed solid tumor (lymphoma is included in this category) that is locally recurrent or metastatic and has progressed on standard treatment • Have left ventricular ejection fraction (LVEF) > lower limit of normal (LLN) as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan evaluation using local institutional standard • Have a documented deleterious *gBRCA* mutation ***(Note: only applicable for patients being screened for enrollment into the RP2D Expansion cohort)*** • Be willing and able to eat a high-fat breakfast on Day 1 of the study **(*Note: only applicable for patients being screened for enrollment into a food-effect PK cohort*)** All patients enrolling into **Part 2 (Phase II portion in OC)** must also meet the following inclusion criteria: • Have a known deleterious *BRCA* mutation (germline or somatic), as determined by a local laboratory that has received an international or country-specific quality standards certification • Have evidence of measurable disease as defined by RECIST Version 1.1 • Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable – Archival tissue from the most recently collected biopsy or debulking surgery should be provided, if available. Otherwise, the next oldest tissue collected should be reviewed until a suitable sample can be provided (at least 20% tumor content with a minimum of 80% nucleated cellular content)

Study Population (cont)	Additional inclusion criteria for patients into **Part 2A (Phase II portion in OC**) include: • Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer – For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology • Have received at least two, but no more than four, prior chemotherapy regimens and have relapsed as confirmed by radiologic assessment a. Last treatment received must have been platinum-based regimen to which patient must have been sensitive (i.e., disease progression occurred at least 6 months after last dose of platinum was administered) b. A maximum of one non-platinum regimen may have been administered. For patients who received four prior regimens, one regimen must have been a non-platinum c. Prior continuous or switch maintenance treatment is permitted (hormonal treatment may be permitted following the last platinum regimen with advance approval from the sponsor) Additional inclusion criteria for patients into **Part 2B (Phase II portion in OC)** include: • Have a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. • Have received at least three, but no more than four, prior chemotherapy regimens and have relapsed disease confirmed by radiologic assessment. – Hormonal agents (e.g., tamoxifen, letrozole, etc), anti-angiogenic agents (e.g., bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc), and other non-chemotherapy agents administered as single agent treatment will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility – Agents administered in the maintenance setting will not be counted as a separate regimen • Have a documented treatment-free interval (TFI) of ≥6 months following the first chemotherapy regimen received. (TFI is determined from the last dose administered as part of primary treatment regimen and not from the last dose of any agent administered in the maintenance setting).

Study Population (cont)	Patients enrolling into **Part 3 (Phase II PK portion in patients with any advanced solid tumor)** must meet the following inclusion criteria: • Have an advanced solid tumor (inclusive of lymphoma) • Have a known deleterious *BRCA* mutation (*gBRCA* or somatic *BRCA [sBRCA]*) (as determined by a local laboratory that has received an international or country-specific, quality standards certification) • Have evidence of measurable disease as defined by RECIST Version 1.1 • Be willing and able to fast, and to eat a high-fat breakfast on Day -7 or Day 1 of the study • Have sufficient archival FFPE tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable – Archival tissue from the most recently collected biopsy or debulking surgery should be provided, if available. Otherwise, the next oldest tissue collected should be reviewed until a suitable sample can be provided (at least 20% tumor content with a minimum of 80% nucleated cellular content) **Exclusion Criteria** Patients enrolling into **either Part 1 (Phase I portion), Parts 2 or 3 (Phase II portions)** will be excluded from participation if any of the following criteria apply: • Active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may be (but not necessarily) currently receiving treatment – Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed >6 months prior and/or bone marrow transplant (BMT) >2 years prior to first dose of rucaparib • Prior treatment with any PARP inhibitor (Part 1, Part 2*)*. Part 3 patients are permitted to have had previous PARPi, if the following conditions are met: a. PARPi was not the most recent treatment, and b. PARPi was discontinued >6 months before first planned dose of rucaparib c. In all study parts, patients who previously received iniparib are eligible • Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks. • Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C. • Received 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 adverse effects from such treatment > NCI CTCAE Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from Sponsor)

Study Population (cont)	• Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of rucaparib • Administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first scheduled dose of rucaparib • 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 • Females who are pregnant or breastfeeding. • For fertile patients (female able to become pregnant or male able to father a child), refusal to use effective contraception during the period of the trial and for 6 months after the last dose of rucaparib • Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, psychiatric disturbance, or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism) • 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 Patients enrolling into **Part 1 (Phase I portion)** will also be excluded from participation if any of the following criteria apply: • Family history of long QT syndrome • Implantable pacemaker or implantable cardioverter defibrillator • Requires treatment with any medication known to produce QT prolongation, with the exception of antiemetics deemed necessary to control nausea (see Appendix C) Patients enrolling into **Part 2B (Phase II OC portion)** will also be excluded from participation if any of the following criteria apply: • Hospitalization for bowel obstruction within 3 months prior to enrollment Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Patients of reproductive potential (female able to become pregnant or male able to father a child) must practice a highly effective method of contraception during treatment and for 6 months following the last dose of rucaparib. No waivers of 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	Rucaparib tablets (40 mg, 60 mg, 120 mg, 200 mg, 300 mg [as free base]) will be supplied to study sites by the sponsor. Each dose should be taken with 8 oz (240 mL) of room temperature water. With the exception of Day -7 and Day 1 of any food-effect PK portions of the study, patients may take rucaparib on an empty stomach or with food. Administration conditions may be revised based on results from food-effect PK evaluation. In Part 1, patients will ingest rucaparib once, twice, or three times a day through Day 21 of Cycle 1 (Safety and PK Assessment Period). Daily treatment with oral rucaparib will continue starting on Day 1 of Cycle 2 for patients continuing in the optional Treatment-Extension Period. In Part 2 and Part 3 (Phase II portion), the starting dose of rucaparib is 600 mg BID administered for continuous 21 day cycles (See Section 3.2.2 for additional details regarding selection of the RP2D). Dose reductions are not permitted during Cycle 1 for all patients in Part 1. Dose reductions for Part 1 patients in Cycle 2 and beyond, and for patients in Parts 2 and 3, are permitted in the event of unacceptable toxicity. Up to three dose reduction steps are allowed. If a patient continues to experience toxicity after three dose reduction steps, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor. Intrapatient dose escalation in Part 1 of the study will be permitted after a patient completes at least 2 cycles of treatment at their initial dose level without experiencing significant drug-related toxicity, provided the dose level to which the patient will escalate has been evaluated and deemed tolerable at the time of the proposed dose increase, and represents ≤100% increase in total dose. The dose may be increased at the beginning of the next cycle. There is no limit to the number of dose escalations steps permitted for an individual patient provided all criteria are met. All dose escalation steps must be approved by the Sponsor's Medical Monitor.
Concomitant Medications	Concomitant anticancer therapies of any kind are not permitted with the exception of ongoing hormonal treatment for prior breast cancer. Supportive care (e.g., antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. For patients undergoing extensive ECG assessments in Part 1, medications known to produce QT prolongation should not be used, with the exception of necessary antiemetic medications. A list of prohibited medications and antiemetic medications requiring additional ECG monitoring is provided in Appendix C of the protocol. Preferable antiemetics for patients in Part 1 include phenothiazines and corticosteroids. Administration of prophylactic antiemetics is prohibited during Cycle 1 of treatment for all patients in Part 1. Caution should be used for concomitant medicines that are substrates of CYP2C19, CYP2C9, and/or CYP3Aand have a narrow therapeutic range (Appendix D). Caution should be exercised in patients receiving oral rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro.

Withdrawal Criteria	A patient must be discontinued from protocol-prescribed therapy if <u>any</u> of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative • Progression of patient's underlying disease • 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 • A positive pregnancy test at any time during the study • Increase in QT/QTc of >60 msec over baseline or QTc >500 msec
Pharmacokinetic Assessments	All patients enrolled in Part 1 and Part 3 (food-effect PK evaluation cohorts only) will have extensive PK sampling prior to and/or during Cycle 1, with collection time points predose and from 15 min through 24 h postdose. For Part 1 patients in Cycles 2-9, only single trough-level PK samples will be collected during each treatment cycle. For Part 2 and Part 3 patients, single trough-level PK samples will be collected at Cycle 1, Day 15 (Part 2 only) and at the end of treatment Cycles 1, 2, 4, 6, and 8. A profile of circulating metabolites of rucaparib at steady state will be evaluated in the first three patients enrolled in the RP2D Expansion cohort (Part 1 only). Serum alpha-1 acid glycoprotein (AAG) sampling will occur on the same day as PK plasma collection (Parts 2 and 3). PK evaluation will be based on the determination of the following parameters for oral rucaparib including (but not limited to): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and k_{el}, V_{ss}/F, and Cl/F. A central/core laboratory will be used for the PK assay.
Tumor Tissue Samples	<u>Part 1</u>: Archival tumor tissue and/or fresh tumor biopsy samples at screening, as well as biopsy sample at time of disease progression/discontinuation of treatment, are optional. <u>Part 2:</u> Archival tumor tissue samples will be collected from all newly enrolled patients and from previously enrolled patients who provide appropriate consent; a biopsy sample at screening and/or time of disease progression/discontinuation of treatment is optional. <u>Part 3:</u> Archival tumor tissue samples will be collected; a biopsy sample at time of disease progression/discontinuation of treatment is optional
Electro-cardiogram Assessments	Patients in Part 1 will have ECGs at screening, at several time points prior to (food-effect PK evaluation cohorts only) and/or during Cycle 1, on Day 1 of every cycle thereafter, and at the end-of-treatment visit. Patients in Part 2A will have ECGs at screening, on Day 1 of each cycle, and at the end-of-treatment visit. Patients in Part 2B and Part 3 have ECGs at screening and at the end-of-treatment visit.

Efficacy Assessments	Efficacy measures will include tumor assessments, consisting of clinical examination and appropriate imaging techniques (preferably computed tomography (CT) scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (magnetic resonance imaging (MRI), X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. Tumor assessments will be performed at screening; prior to the start of Cycles 3, 5, and 7; and prior to the start of every three cycles of treatment thereafter, beginning with Cycle 10. For Part 2B patients discontinued from study treatment for reason other than disease progression or death, tumor assessments will continue to be performed during the long-term follow-up period (within 7 days prior to the start of every 9 weeks until radiologically confirmed disease progression, death, or initiation of subsequent treatment). Patients who have been on study for at least 18 months may decrease the frequency of tumor scans to every 16 weeks (±14 days). Confirmatory scans 4–6 weeks after response was documented are required if initial CR or PR was noted prior to the start of Cycle 7 or beyond. CT scans will be collected for all patients enrolled into Part 2 and Part 3 for possible evaluation by independent radiology review.
Tumor Markers	Part 1: tumor markers applicable to a patient's tumor type are optional. Part 2: CA-125 levels will be collected for all patients. Part 3: tumor markers applicable to a patient's tumor type will be analyzed.
Safety Assessments	Safety measures will include AEs, hematology, clinical chemistry, urinalysis, vital signs, body weight, concomitant medications/procedures, ECOG performance status, ECGs, and rucaparib dose modifications.
Statistical Procedures	**Sample Size Justification** The total enrollment planned for this study is approximately 140 patients: 56 patients were enrolled into Part 1 (Phase I portion), up to 41 will be enrolled into Part 2A, approximately 40 patients will be enrolled into Part 2B, and approximately 20 patients will be enrolled into Part 3. Clinical trials of olaparib in relapsed ovarian cancer patients associated with a *gBRCA* mutation demonstrated ORRs of 13-41%.[3-5] For the part of the study evaluating rucaparib in platinum-sensitive, relapsed, high-grade serous and endometrioid epithelial ovarian, fallopian tube, and primary peritoneal cancer associated with a *gBRCA* mutation, an ORR of 20% will be set as the target of interest. **Sample size justification for Part 2A:** The study will use a Simon 2-stage design to evaluate the efficacy of rucaparib in Part 2 (Phase II portion). Initially, 21 patients will be treated in Stage 1 of the study; if two or more patients in Stage 1 have an objective response (CR or PR), then the remaining 20 patients will be treated in Stage 2. If fewer than two patients in Stage 1 have an objective response, then no further patients will be enrolled. Characteristics of the Simon 2-stage design include: • 5% probability of accepting a poor drug • 90% probability of accepting a good drug • ORR of 5% for a poor drug • ORR of 20% for a good drug • A promising drug will have five or more patients with an objective response (CR or PR) out of 41 patients at the end of Stage 2.

Statistical Procedures (cont)

The criteria for Stage 1 success were met in April 2014, and Stage 2 is ongoing with total enrollment of 41 evaluable patients completed in April 2015.

Sample size justification for Part 2B:

An ORR ≥20% in this population would be worthy of further exploration. The table below provides 95% confidence intervals (CIs) for ORRs of 30% to 50% assuming a sample size of 40 patients.

Confidence Intervals for Observed Response Rates

ORR(%)	[95% CI]
30	17,47
40	25, 57
50	34,66

CI=Confidence intervals of ORR using Clopper-Pearson methodology.[6]

Therefore with the sample size of 40 patients an observed ORR of 30% would show similar response as current treatment, however, an observed ORR of 40% or greater has a 95% CI which exceeds the 20%.

Sample size justification for Part 3:

This part of the study will be an initial randomized, single dose, two treatment, two period, crossover design, to explore food effect and other PK parameters; with subsequent continuous BID dosing. It is estimated that enrolling approximately 20 evaluable patients will provide sufficient data for PK analysis.

Pharmacokinetic Analyses

PK parameters will be determined using noncompartmental methods. AUC from Time 0 to the last observation will be calculated using the trapezoid rule. The k_{el} will be calculated using log-linear regression on the terminal part of the concentration time curve. The $t_{1/2}$ and the AUC from the last observation to infinity will be calculated from the estimated k_{el}. Other parameters to be determined are C_{max}, T_{max}, Vss/F, and Cl/F.

The effect of food on PK parameters including (but not limited to) C_{max} and AUC will be compared using analysis of variance (ANOVA) techniques.

Relationship Between PK and QTc

A linear and nonlinear mixed effect modeling approach will be used to quantify the relationship between the plasma concentration and the ΔΔQTc (time-matched, on-treatment to pretreatment difference in QTc interval, baseline-adjusted). Plots of the mean QT/QTc versus drug concentrations and the correlation between concentration and QT variables will be explored.

Metabolite Profiling at the RP2D

Individual pooled plasma samples, one from each of three included patients, will be prepared using the method proposed by Hamilton.[7] The pooled plasma samples will be further processed before being analyzed by high-performance liquid chromatography coupled in-line with ultraviolet spectrophotometric and tandem mass spectrometric detection (HPLC-UV-MS/MS).

Statistical Procedures (cont)	**Efficacy Analysis** The ORR will be summarized with frequencies and percentages. The duration of response for CR and PR patients will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. Response will be determined using RECIST Version 1.1. Kaplan-Meier methodology will be used to summarize time to event variables. **Safety Analyses** Data from all patients who receive at least one dose of rucaparib will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, ECGs, and concomitant medications/procedures will be tabulated and summarized. AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Grade 3 or higher AEs. Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG will be summarized categorically and descriptively.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours
$AUC_{0-\infty}$	area under the curve from time zero to infinity
AUC_{0-t}	area under the curve from time zero to time t
BER	base excision repair
BID	twice a day
BMT	bone marrow transplant
BRCA1	breast cancer 1
BRCA2	breast cancer 2
BUN	blood urea nitrogen
CA-125	cancer antigen-125
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	apparent total plasma clearance after oral administration
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSB	double-strand break
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end -of- study
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
HDL	high density lipoprotein
GALT	gut-associated lymphoid tissue
gBRCA	germline *BRCA*
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
HGSOC	high-grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC-UV-MS/MS	high-performance liquid chromatography coupled with ultraviolet spectrophotometric and tandem mass spectrometric detection
HR	homologous recombination
HRD	homologous recombination deficiency
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
iv	Intravenous
k_{el}	elimination rate constant
LDL	low density lipoprotein
LLN	lower limit of normal
LOH	loss of heterozygosity
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NOAEL	no-observed-adverse-effect level
OC	ovarian cancer

ORR	overall response rate
OS	overall survival
PARP	poly(adenosine diphosphate [ADP]-ribose) polymerase
PARPi	poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
QD	once a day
QTcF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
sBRCA	somatic *BRCA*
SD	stable disease
SOC	system organ class
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TID	three times a day
T_{max}	time to maximum concentration
TMZ	Temozolomide
TFI	treatment-free interval
ULN	upper limit of normal
V_{ss}/F	apparent volume of distribution at steady state after non-iv administration
WBC	white blood cell

3 INTRODUCTION

3.1 DNA Repair and Cancer Therapy

Deoxyribonucleic acid (DNA) is constantly damaged by environmental factors such as sunlight and DNA-binding chemicals. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs), which are normally quickly repaired by a process known as base excision repair (BER). This process is initiated by the activity of the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzyme.[8] During normal cell cycling, DNA is replicated and replication forks are eventually stalled by persistent SSBs. If stalled replication forks are not rapidly repaired, they can often degenerate and form DNA double-strand breaks (DSBs), which are highly likely to be lethal to the cell.[3] In normal cells, an additional DNA repair process known as homologous recombination (HR) can repair DSBs.[3] HR is mediated by breast cancer 1 and 2 genes (*BRCA1* and *BRCA2*) and acts as a functional buffer to enable normal cells to survive the effects of PARP and BER inhibition.[3] Homologous recombination defects or PARP inhibition on their own can be withstood by a cell, but the combination is fatal, a concept termed "synthetic lethality".[3-5]

Mutations in *BRCA1* and *BRCA2* have been identified as a cause of hereditary breast and ovarian cancer,[9] accounting for about 60% of inherited breast cancer and a smaller percent of ovarian cancer.[10] These patients carry heterozygous deleterious mutations in their germline DNA, and develop tumors when the remaining wild-type functional allele is inactivated (i.e., "second hit"). Interestingly, approximately 51% of high-grade serous ovarian cancers have genetic alterations in DNA repair pathways, commonly involving germline and somatic defects in *BRCA*.[11]

Synthetic lethality has been exploited in two proof-of-concept clinical trials with an oral PARP inhibitor in patients with BRCA-deficient tumor types. These trials evaluated the efficacy of continuous oral dosing in women with confirmed germline *BRCA1* or *BRCA2* mutations, and either ovarian cancer or advanced breast cancer.[12, 13] In these patients, who had received a median of three prior chemotherapy regimens, encouraging overall response rates (ORRs) of 33% and 41%, respectively, were observed.

In addition to use as monotherapy to drive synthetic lethality in the context of a *BRCA* mutation,[12-14] PARP inhibitors have been administered in combination with cytotoxic agents (and radiation) in vitro and in vivo.[15-18] In particular, DNA damaging agents such as temozolomide (TMZ), irinotecan, and platinums have been shown to synergize with PARP inhibitors in nonclinical experiments.[19-21] The explanation offered is that PARP inhibition limits the ability of the cell to repair "therapeutic" DNA damage and thus potentiates the therapeutic effect of the co-administered chemotherapy.

3.2 Background

Rucaparib (CO-338; formerly known as PF 01367338 and AG 14699) is a small molecule inhibitor of PARP that has been in clinical development since 2003. Initial animal model studies evaluating rucaparib administered in combination with chemotherapeutic agents (e.g., TMZ) suggested that a dose-dependent inhibition of PARP activity correlated with antitumor activity. Hence, the initial clinical program assessed safety and efficacy in patients with malignancies

commonly treated with selected chemotherapeutic agents. Initial Phase I and Phase II clinical studies were conducted with an intravenous formulation of rucaparib administered in combination with a variety of chemotherapeutic agents. An oral formulation as monotherapy is the focus of current development efforts.

Nonclinical evaluation has also demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous cell lines to rucaparib, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with deficiencies of *BRCA1* and *BRCA2*.

Details of ongoing/completed studies and other nonclinical experiments are provided in the Investigator's Brochure.

3.2.1 Nonclinical Experience

3.2.1.1 Rucaparib Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics (PK) and toxicokinetics of rucaparib following oral administration of the camsylate salt, the intended route of administration in humans, was evaluated in the mouse, rat, and dog. The time at which the peak plasma concentrations were observed (T_{max}) occurred at 1 – 3 hours post-dose in the mouse and dog, with the rat generally exhibiting a later T_{max} (4 – 8 hours). The oral bioavailability was 17%, 36%, and 62% respectively, in the mouse (50 mg/kg), rat (100 mg/kg), and dog (20 mg/kg). In the rat and dog, there were no marked gender-related differences and no accumulation after repeat oral administration. A less than dose-proportional increase in exposure was observed in the rat and dog when rucaparib was administered as a suspension in 0.5% methylcellulose; however, a greater than dose-proportional increase in exposure was observed in the 1-month dog toxicity study when rucaparib was administered in capsules.

Quantitative whole-body autoradiography studies in rats showed that [^{14}C] rucaparib radioequivalents were rapidly and widely distributed to tissues following intravenous administration, consistent with the large volume of distribution. At 2 min after dosing, the highest concentrations were found in the kidney, lung, thyroid gland, heart, stomach mucosa, liver, adrenal glands, spleen, and blood. Little radioactivity was present in brain; none was detected at 15 min after dosing. Activity was undetectable in most tissues by 96 hours after dosing, however levels in the choroid/retina declined more slowly, and persistent radioactivity was also found in hair follicles through 192 hours, indicating that drug equivalents have high affinity and long half-life in pigmented tissues. High levels of radioactivity were observed in ureters, bladder, and bile ducts, indicating both renal and biliary routes eliminated drug equivalents.

In vitro studies indicated that rucaparib reversibly inhibited (in order of decreasing potency) CYP1A2, CYP2C19, CYP2C9, CYP3A, CYP2C8, and CYP2D6. Rucaparib also moderately inhibited uridine diphosphate-glucuronosyletransferase (UGT) 1A1. Rucaparib demonstrated concentration-dependent induction of CYP1A2 and downregulation of CYP3A4 and CYP2B6 at clinically relevant concentrations in a hepatocyte incubation study. No time-dependent CYP inhibition was observed.

Based on in vitro CYP interaction data, the drug-drug interaction (DDI) potential of rucaparib as a CYP inhibitor and/ or inducer was assessed by calculating the ratio of AUC (AUCR) of CYP substrate drugs in the presence and absence of rucaparib at target clinical exposures (600 mg BID) using the mechanistic static modeling.[22, 23] AUCR allows a conservative estimation of the magnitude of DDIs. Based on this analysis, the DDI potential for rucaparib was estimated to be moderate (AUCR 2 to 5) for CYP3A (AUCR=5.0), CYP1A2 (AUCR=2.9), CYP2C8 (AUCR=2.6), and CYP2D6 (AUCR=2.3); but appeared to be strong (AUCR > 5) for CYP2C19 (AUCR=11) and CYP2C9 (AUCR=5.2). Clinical implication of CYP3A downregulation was unknown and thus not considered in the modeling. However, the downregulation could further increase AUCR for CYP3A and result in elevated exposures of drugs that are CYP3A substrates.

Based on bi-directional experiments of digoxin transport carried out using Caco-2 cells, it was determined that rucaparib is a moderate P-glycoprotein (P-gp) inhibitor. Patients taking dixogin should have their dixogin levels monitored regularly according to standard institutional practices.[22, 23]

Rucaparib protein binding was determined in the human, dog, rat, and mouse plasma over a concentration range of 0.5 to 100 µM. In humans, the percent protein bound ranges from 54.6% to 74.9%. The percent protein bound ranges from 58.1% to 65.2%, 53.4% to 60.2%, and 49.5% to 73.4% in mouse, rat, and dog plasma, respectively.

3.2.1.2 Multiple-Dose Toxicity Studies

Rucaparib was evaluated in both rat and dog in oral and IV infusion toxicity studies. Only the multiple-dose toxicity studies utilizing the oral formulation are summarized below. Details of all other toxicity studies are provided in the Investigator's Brochure. Target organs identified in studies where rucaparib was administered orally include the hematopoietic system and gastrointestinal tract. No cardiovascular findings were noted in any of the oral toxicity studies

Multiple-Dose Oral Toxicity in Rats

Administration of rucaparib camsylate salt via oral gavage was generally well-tolerated in the rat up to 1000 mg/kg/day for 7 days and up to 150 mg/kg/day for 28 days. Decreases in body weight gain and food consumption were noted in both studies. In the 7-day study, target organs identified microscopically were bone marrow, spleen, and thymus. Minimal to mild bone marrow hypocellularity was noted in all dose groups. The no-observed-adverse-effect-level (NOAEL) was established at 500 mg/kg/day.

In the 28-day study, there were 3 rucaparib-related deaths at 500 mg/kg/day immediately after blood collection on Day 28 (n=1) or Day 29 (first day of recovery phase (n=2). These deaths likely resulted from the marked anemia identified hematologically. Other rucaparib-related clinical signs at 500 mg/kg/day included thinning haircoat and pale eyes. Identified target organs included bone marrow, spleen, lymphoid tissue (thymus, gut-associated-lymphoid tissue [GALT], and lymph nodes), and cecum (at 500 mg/kg/day only). Following cessation of rucaparib dosing, most findings reversed. In this study, the severe toxic dose in 10% of the animals (STD10) was 500 mg/kg/day and the NOAEL was 50 mg/kg/day.

Multiple-Dose Oral Toxicity in Dogs

Oral gavage administration of the camsylate salt form of rucaparib to dogs for 7 days resulted in gastrointestinal clinical signs at the 80 mg/kg/day high-dose group. Hematopoietic effects of decreased reticulocytes were noted in mid- to high-dose groups and leukopenia was exhibited in all treatment groups. Lymphoid atrophy occurred in both sexes and in all treatment groups. Decreased bone marrow cellularity was seen in both sexes (males at all doses; females at 80 mg/kg/day). A 7-day repeat-dose toxicity study using oral capsules in dogs was repeated in order to characterize the toxicity of a new lot of rucaparib camsylate. Similar to the results of the prior 7-day study in dog, gastrointestinal clinical findings were noted at 80 mg/kg/day. Vomiting was observed throughout the dosing phase for males as well as liquid and/or mucoid feces in both genders. Decreased food consumption was observed at 80 mg/kg/day that correlated with the body weight loss that was considered adverse. Decreases in erythroid, platelet, and leukocyte parameters were observed primarily at 80 mg/kg/day and occasionally at 20 or 5 mg/kg/day. These data indicated that the drug targeted multiple bone marrow lineages in a dose-related pattern.

Rucaparib camsylate salt in capsules was administered orally to dogs for 30 consecutive days with a 29-day recovery. Gastrointestinal clinical signs were noted at≥ 5 mg/kg/day, with decrease in food consumption at 75 mg/kg/day. Adverse hematological changes (decrease in erythroid, myeloid, and megokaryocytic lineages) occurred at≥ 20 mg/kg/day. Effects were fully reversible. The NOAEL in this study was 5 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to dogs at doses of 3, 15/10, 40/30/20 mg/kg/day for 91 consecutive days with a 29-day recovery period. Body weight losses and inappetance observed at the high dose in both sexes during the first quarter of the dosing phase were considered adverse and resulted in dose reductions (40 to 30 to 20 mg/kg/day for toxicity and 15 to 10 mg/kg day in order to maintain multiples of exposures for optimal testing of dose response) for the remainder of the study. Clinical pathology findings were indicative of bone marrow toxicity; these changes were non-progressive over time suggesting potential adaptation to these initial effects. Hematological findings at 40/30/20 mg/kg/day correlated with erythroid atrophy of the bone marrow detected microscopically. By Day 29 of recovery, most effects reversed. The highest non-severely toxic dose (HNSTD) for this study was 20 mg/kg/day for male dogs. No HNSTD was established for female dogs. The NOAEL was 10 and 20 mg/kg/day for male and female dogs, respectively.

3.2.1.3 Additional Observations

In vitro genetic toxicology assays demonstrated oral rucaparib to be clastogenic. Bacterial mutagenicity data for rucaparib were clearly negative in four microbial tester strains, both with and without metabolic activation, and equivocal in a fifth tester strain.

In an in vitro assay for human ether-a-go-go-related gene channel blockade (hERG) activity, the IC_{20} and IC_{50} values for the inhibitor effects of rucaparib (50% inhibitor concentration and 20% inhibitory concentration) on the hERG potassium currents were 7 (2264 ng/mL) and 24 μM (7761 ng/mL), respectively. These values are 9-fold and 2.6-fold higher, respectively, than the mean unbound steady state plasma concentration (858 ng/mL) observed to date in humans at a

dose of 600 mg BID rucaparib administered orally. Effects on appearance and behavior, motor activity, body temperature, and a number of neurofunctional tests and reflexes were evaluated in rats. A dose of 50 mg/kg of rucaparib administered via IV infusion (mean C_{max}=13629 ng/mL) resulted in a significant reduction in motor activity compared with vehicle-treated animals; however, there were no effects on neurofunctional or reflex testing at this dose. The plasma concentration measured at this dose is 4.7-fold above the mean steady state plasma concentration (2880 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Administration of rucaparib to Long-Evans rats orally at doses up to 750 mg/kg/dose, followed by a single exposure to solar-simulated ultraviolet radiation approximately 4 hours after the final dose elicited no skin or ocular reactions indicative of phototoxicity. The no-observed-effect-level (NOEL) for phototoxicity was >750 mg/kg/day.

Complete information on the preclinical PKs and drug metabolism of rucaparib may be found in the current Investigator's Brochure.

3.2.2 Clinical Experience

The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents. Initially, the IV formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts.

Additional information regarding clinical studies with rucaparib is available in the Investigator's Brochure.

3.2.2.1 Rucaparib Monotherapy

Rucaparib monotherapy is currently being evaluated in the treatment setting for relapsed ovarian cancer in two Clovis-sponsored clinical studies: Study CO-338-017 (ARIEL2) and this study, CO-338-010. Over 200 patients have been treated with the oral formulation of monotherapy rucaparib in open-label trials; over 150 patients have been treated with the recommended Phase 2 dose of 600 mg BID.

This Clovis-sponsored study CO-338-010 is a 3-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered daily for continuous 21-day cycles, initiated in Q4 2011. Fifty-six patients enrolled into Part 1 of the study (median age 50 yrs [range 21–71]; 51 female; 27 breast cancer, 20 ovarian/peritoneal cancer, 9 other tumor) have been treated at dose levels of 40, 80, 160, 300, and 500 mg once daily (QD), and 240, 360, 480, 600, and 840 mg twice daily (BID) rucaparib administered continuously. Two patients are still receiving treatment as of December 2014. One of 6 patients treated with 360 mg BID rucaparib experienced a dose-limiting toxicity (DLT) of Common Toxicity Criteria for Adverse Events (CTCAE) Grade 3 nausea despite maximal intervention; no DLTs were observed in the 480 (n=9), 600 (n=5), or 840 mg BID (n=3) cohorts during Cycle 1.

In the ongoing Phase 2 portion (Part 2A), 40 ovarian cancer patients (median age 55 [range 42-84]; ECOG performance status 0/1=16/24; median number of anticancer regimens=2 [range 2-4]; were enrolled as of April 2015.

In the ongoing CO-338-017 (ARIEL2) trial, 204 ovarian cancer patients (median age 65 [range 31-86]; ECOG performance status 0/1/pending=137/61/7; median number of anticancer regimens=1 [range 1-6); median number of platinum-based regimens=1 [range 1-5]) have enrolled into Part 1 of the study as of December 2014; enrollment into Part 1 completed.

Safety

As of November 2014, safety data are available for n=163 ovarian cancer patients treated with 600 mg BID rucaparib monotherapy in the ongoing Phase 2 studies, including Part 1 of this trial. Treatment-related adverse events (all grades) reported in ≥15% of patients include: gastrointestinal and related events (nausea, vomiting, dysgeusia, diarrhea, abdominal pain, and decreased appetite); anemia; fatigue/asthenia, and headache. Elevations of ALT and/or AST are also commonly observed. The ALT/AST elevations occur early (within first 2-4 weeks of treatment), are generally mild to moderate (Gr 1-2), are not accompanied by any changes in bilirubin levels, and are often transient, and resolve to within normal ranges, or stabilize. No patient has met the laboratory criteria for Hy's Law.[24] As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. Grade 3/4 adverse events assessed as treatment-related and occurring in >5% of patients include: anemia/decreased hemoglobin and increased ALT. All treatment-related adverse events have been successfully managed with concomitant medications, and treatment interruption and/or dose reduction. No patient has discontinued rucaparib treatment due to a treatment-related adverse event. A total of five patients have died on study or within 30 days of last dose of rucaparib; all deaths were due to disease progression and were assessed as not related to rucaparib.

Extensive centrally-reviewed electrocardiogram (ECG) monitoring was conducted in the Phase 1 portion of study CO-338-010. ECG results (as triplicate reads) are available for all 56 treated patients. No patient had a QTcF measurement ≥500 msec at any time during study participation. Only one patient had a QTcF measurement ≥480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient has continued to receive monotherapy rucaparib at a dose of 480 mg BID with no further QTcF measurement ≥480 msec. No patient experienced a ≥60 msec increase in QTcF over baseline. A total of 11 patients experienced a QTcF increase ≥30 msec over baseline. Further analyses suggest a lack of relationship between QTcF increase ≥30 msec and dose or exposure. In addition, there were no adverse events suggestive of cardiac arrhythmia (e.g., presyncope, syncope, sudden death) in any patient. ECG and adverse event data to date in patients receiving monotherapy rucaparib at doses up to 840 mg BID suggest there is a minimal risk of QTc prolongation.

Efficacy

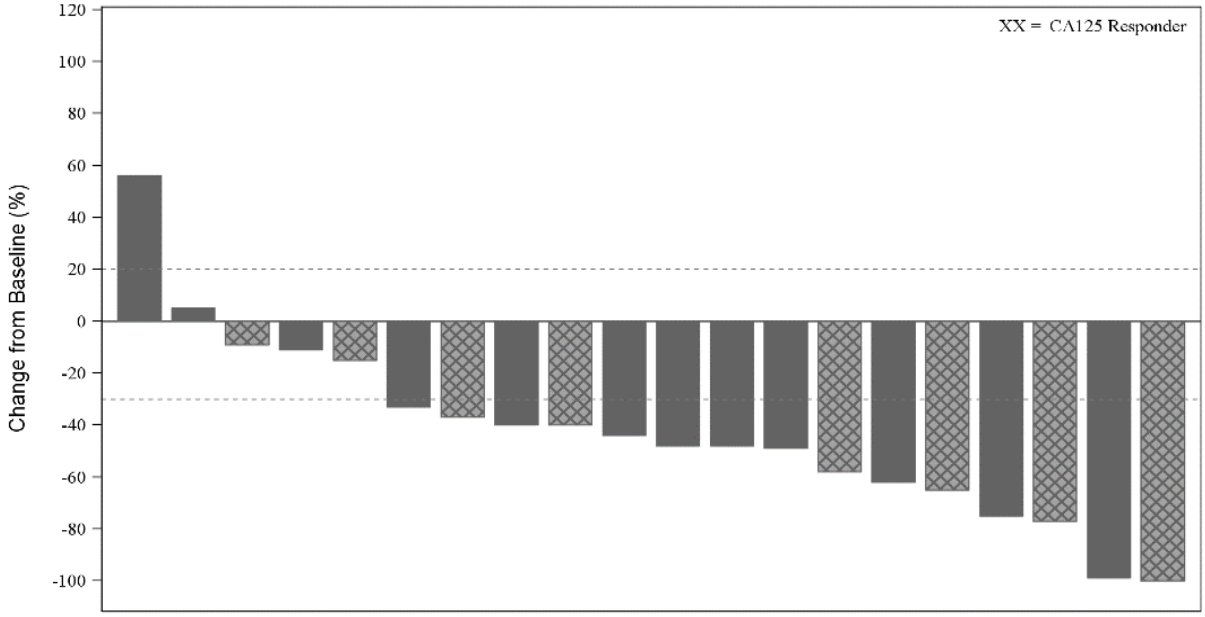
In the Phase 1 portion, 2 patients (breast cancer and ovarian cancer, both *gBRCA*^{mut}) achieved a RECIST CRs and 7 patients (3 ovarian cancer, 4 breast cancer, 1 pancreatic cancer; all

gBRCA^{mut}) achieved a RECIST PR during the dose escalation phase (n=2 at 300 mg QD; n=2 at 360 mg BID; n=3 at 480 mg BID; and n=2 at 600 mg BID). Responses were durable across tumor types. In addition, 3 patients with ovarian cancer achieved a cancer antigen 125 (CA-125) response as defined by Gynecologic Cancer InterGroup (GCIG) criteria. The disease control rate (CR, PR, or SD>12 weeks) in evaluable ovarian cancer patients treated at doses ≥360 mg BID was 92% (11/12). Responses were observed in platinum-resistant as well as platinum-sensitive ovarian cancer patients. In platinum-resistant ovarian cancer patients treated with ≥360 mg BID rucaparib, 50% (4/8) achieved either a RECIST (25%, 2/8) or GCIG CA-125 response (25%, 2/8). The disease control rate (CR, PR, or SD>24 weeks) in this group was 75% (6/8) and median time on treatment was approximately 9 months (range 1.5-14.5).

In the Phase 2 portion of Study CO-338-010 (Part 2A) in ovarian cancer patients, compelling activity has been observed in patients who had received 2-4 prior chemotherapy regimens and a deleterious *BRCA* mutation, with 15 of 20 (75%) achieving a RECIST PR and 17 of 20 (85%) achieving a RECIST PR and/or a GCIG CA-125 response. The vast majority of patients had some level of target lesion measurement reduction as shown in Figure 1.

Figure 1 Best Target Lesion Response – Study CO-338-010 Phase 2 (Part 2)

Best Response in % Change From Baseline Longest Sum of Diameters
Study CO-338-010
Phase 2 Patients (Rucaparib 600 mg BID)



The efficacy of rucaparib in ovarian cancer patients with a deleterious *BRCA* mutation (germline or somatic) who received ≥3 prior chemotherapy regimens and were treated with 600 mg BID rucaparib in Studies CO-338-017 (ARIEL2) and Part 2A of CO-338-010 has been evaluated. In this group, which included both patients with platinum-sensitive and platinum-resistant disease, ORRs of 47% (RECIST) and 73% (RECIST & GCIG CA-125) have been observed, suggesting that rucaparib may be a suitable treatment alternative in this patient population with advanced disease and limited treatment options.

Pharmacokinetics

After once daily oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. T_{max} and $t_{1/2}$ were independent of dose. Steady state exposure increased by an average of 89%, consistent with accumulation expected for a compound exhibiting a $t_{1/2}$ of approximately 17 hours administered once daily. Following BID oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. Moreover, BID dosing delivered a lower C_{max} with a low peak to trough plasma concentration variation. The target trough level of 2 μM was achieved in 100% of patients (n=23) at ≥240 mg BID with low inter-patient variability (≤5-fold) within each dose group. Steady state trough levels also exhibited low intra-patient variability (24% CV). No sporadically high exposures were observed. The effect of food on rucaparib PK was evaluated at 40 mg (n=3) and 300 mg (n=6) doses administered once daily. There was no food effect; patients may take rucaparib on an empty stomach or with food.

3.2.2.2 Recommended Phase II Dose (RP2D) of Rucaparib Monotherapy

The dose of 600 mg BID rucaparib was selected as the recommended dose for Part 2 and Part 3 of this study based on the overall safety & tolerability, PK, and clinical activity profile observed in the dose-escalation phase of this trial. There was one DLT at 360 mg BID and none at higher dose levels; however, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1. In addition, a rucaparib exposure plateau was observed at total daily doses ≥960 mg (480 mg BID). This is well above the dose (300 mg QD) at which activity was first observed and the modeled activity threshold based on clinical activity of other PARP inhibitors and rucaparib trough levels. Taken in total, these data support the selection of 600 mg BID as the RP2D for the Phase II portion of this study.

Study A4991002, Study A4991014 and Study A4991005

Further details of these Phase I (Study A4991002 and Study A4991014) and Phase II (Study A4991005) studies are provided in the Investigator's Brochure.

3.2.2.3 Absorption, Distribution, Metabolism, and Elimination

PK data are available for a total of 136 patients: 23 from Study A4991002 (30 min intravenous infusion), 62 from Study A4991014 (32 with 30 min intravenous infusion and oral dosing; 30 with oral dosing only), and 51 from Study CO-338-010 (oral dosing). Results indicate that the free base of rucaparib, after a 30 min intravenous infusion of rucaparib alone, declined in a multi-exponential manner with a mean (CV %) terminal half-life of about 13.5 h (58). The mean (CV %) total plasma clearance was 18.7 L/hours (48), which is approximately 25% of hepatic blood flow. The mean (CV %) Vd_{ss} was 276 L (64), indicating distribution into tissues. The area under the curve (AUC) and C_{max} of rucaparib increased proportionally with the intravenous dose, indicating linear PKs over the dose range up to 40 mg. Approximately 50% accumulation of rucaparib was observed after 4 days of multiple intravenous dosing.

Following administration of a single intravenous dose of rucaparib alone, mean (CV %) 24 h urine recovery of rucaparib was 10.5% (41), indicating that renal elimination is not the major elimination pathway of rucaparib.

After single oral administration, rucaparib was rapidly absorbed with C_{max} generally achieved within 2.5 - 4 h. Following attainment of C_{max}, plasma concentrations of orally administered rucaparib declined in a multiple exponential manner. Dose-proportional increase in C_{max} and AUC_{0-24} was generally observed at doses up to 600 mg BID. Apparent terminal half-life after the oral rucaparib dose was similar to that after intravenous administration. The mean absolute bioavailability of the rucaparib immediate release tablet was estimated to be 36%.

Results of genotyping data indicate that the exposure measured by the AUC from time zero to 24 h (AUC_{0-24}) were similar between extensive and poor metabolizers of both CYP2D6 and CYP3A5 enzymes. These CYPs were chosen for analysis because CYP2D6 shows genetic polymorphisms, and CYP3A5 appears to be an important genetic contributor to interindividual and interracial differences in CYP3A-dependent drug metabolism.

3.3 Rationale for Study

Over the past decade there has been little improvement in the cure rate of ovarian cancer. The combination of carboplatin and paclitaxel is an effective standard first-line therapy with responses observed in the vast majority of patients but unfortunately most patients will eventually relapse. Although initial recurrences are also still frequently platinum-sensitive (i.e. disease relapse occurs >6 months after the last dose of platinum), most patients will eventually develop resistance to platinum-based chemotherapy, thus there remains a significant need for additional treatment options.

Recent studies have shown that PARP inhibitors provide meaningful clinical benefit for relapsed ovarian cancer patients who are known to harbor a *BRCA* mutation and that the benefit is enhanced in the platinum sensitive group.[13, 25, 26] Rucaparib is a potent small molecule inhibitor of PARP1 and PARP2 being studied in cancer indications, such as ovarian, that are associated with a defect in homologous recombination DNA repair.

The first objective in this study was to determine the optimal monotherapy dose and schedule for orally administered rucaparib. As described in Section 3.2.2, 600 mg BID has been selected as the rucaparib RP2D based on overall safety & tolerability, PK, and the clinical activity profile. Responses have been observed in patients with ovarian, breast and pancreatic patients harboring a *BRCA* mutation. The data generated with rucaparib and other PARP inhibitors, suggest that platinum-sensitive ovarian cancer patients who harbor a *BRCA* mutation may benefit from treatment with a well-tolerated PARP inhibitor, such as rucaparib.

The Phase II portion (Part 2A) established robust efficacy of the RP2D of rucaparib (600 mg BID) in this patient population: the criteria for Stage 1 success were met in April 2014, and Stage 2 enrollment of 41 patients was completed in April 2015. In this initial cohort the median number of prior treatments was 2 [range 2-4]. Cohort 2B will characterize the signal in a later line sub-population, where unmet need is greatest. Other than the requirement for 3-4 previous treatment lines, the demographic and baseline characteristics of cohorts 2A and 2B are similar.

Therefore, overall, part 2 of the study will provide a comprehensive evaluation of the efficacy of rucaparib in advanced ovarian cancer patients with a germline and/or tissue, deleterious *BRCA* mutation. The Phase II PK portion (Part 3) will evaluate the PK profile of 300 mg dose strength tablets in the fed versus fasted state, in an exploratory food effect assessment and at steady state and also assess the safety and tolerability, and anti-tumor activity of the higher dose strength tablets.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

This is a three-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered once, twice, or three times a day for continuous 21-day cycles:

- Part 1 is the Phase I portion in patients with locally advanced or metastatic solid tumors, including lymphoma, who have progressed on standard therapy. Patients enrolled into the Part 1 RP2D Expansion must also have a documented deleterious *gBRCA* mutation.
- Part 2A is a Phase II portion in patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *gBRCA* mutation.
- Part 2B is a Phase II portion in patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with evidence of a deleterious *BRCA* mutation (germline or somatic).
- Part 3 is a Phase II PK portion to evaluate higher dose strength tablets in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a *BRCA* mutation (germline or somatic).

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

Table 1. Primary and Secondary Objectives and Endpoints

Primary Objectives	Primary Endpoints
1. To evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumors, and to determine the MTD and RP2D ***(Part 1 only)***	1. The incidence of Grade 3 or 4 AEs and clinical laboratory abnormalities defined as DLTs
2. To characterize the PK profile of oral rucaparib when administered as a continuous daily dose ***(Part 1 and Part 3 only)***	2. PK parameters: area under the curve from time zero to the time with the last measurable concentration (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), C_{max}, time to maximum concentration (T_{max}), elimination half-life ($t_{1/2}$), elimination rate constant (k_{el}), apparent volume of distribution at steady state after non-iv administration (V_{ss}/F), and apparent total plasma clearance (Cl/F)
3. To evaluate ORR in patients with relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *BRCA* mutation ***(Part 2 only)*** [henceforth abbreviated to ovarian cancer (OC) population]	3. ORR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1; secondary analysis including GCIGCA-125 criteria

Table 1. Primary and Secondary Objectives and Endpoints	
Secondary Objectives	**Secondary Endpoints**
1. To characterize the single-dose PK profile of oral rucaparib after a high-fat breakfast compared to that in the fasted state ***(Part 1 and Part 3 only)***	1. PK parameters C_{max} and AUC (fasted and fed)
2. To evaluate the effects of oral rucaparib on the QT/QTc interval measured by ECG ***(Part 1 only)***	2. Change from baseline in QT/QTc interval
3. To evaluate the safety and tolerability of oral rucaparib ***(Parts 1, 2, and 3)***	3. The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
4. To evaluate duration of response in the OC population ***(Part 2 only)***	4. Duration of response per RECIST v1.1.
5. To evaluate antitumor activity of oral rucaparib in various solid tumors ***(Part 1 and Part 3 only)***	5. Response per RECIST v1.1; additional analyses including applicable tumor markers
6. To assess progression-free survival (PFS) in the OC population ***(Part 2 only)***	6. PFS defined as the time to first occurrence of disease progression per RECIST v1.1 or death
7. To evaluate survival ***(Part 2B only)***	7. Overall survival (OS)

Table 2. Exploratory Objectives and Endpoints	
Exploratory Objectives	**Exploratory Endpoints**
1. To explore the relationship between the PK of oral rucaparib and the potential changes in QT/QTc interval ***(Part 1 only)***	1. QT/QTc interval correlated with plasma concentrations of oral rucaparib
2. To profile circulating metabolites of oral rucaparib at steady state at the RP2D ***(Part 1 only)***	2. Metabolic profile in the Day 15 plasma samples
3. To explore the association between genomic alterations identified in tumor tissue and clinical outcome (Part 1, 2, and 3)	3. Mutational status of *BRCA1/2* and other homologous recombination genes. Genomic scarring/ loss of heterozygosity (LOH) assessment in tumor tissue and response by RECIST v1.1 and/or tumor markers (ie, CA-125)

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a 3-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered once, twice, or three times a day for continuous 21-day cycles. Part 1 is a Phase I portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. Part 2A is a Phase II portion in patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *gBRCA* mutation who have progressed after at least two, but no more than four, prior regimens. Part 2B is a Phase II portion in patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with evidence of a deleterious *BRCA* mutation (germline or somatic) who have received at least three, but no more than four, prior chemotherapy regimens. Part 3 is a Phase II PK portion to evaluate higher dose strength tablets in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a *BRCA* mutation (germline or somatic). Patients will enroll into either Part 1, Part 2, or Part 3 of the study, not in to multiple parts.

5.1.1 Screening Period

All patients will undergo screening assessments within 30 days prior to the first dose of oral rucaparib. Study-procedure-related AEs that occur after signing of the informed consent form and before administration of the first oral rucaparib dose will also be collected during this period.

5.1.2 Part 1 (Phase I Portion)

In Part 1 of the study, there will be an estimated six to twelve dose-escalation cohorts, with a minimum of three patients enrolled in each cohort, and an expanded evaluation of the RP2D in up to 15 patients. Treatment cycles will comprise 21 days of continuous dosing.

The MTD is defined as the maximum daily oral dose at which <33% of patients experience a DLT during Cycle 1 (Safety and PK Assessment Period). If a DLT is observed in one of three patients, then three additional patients will be enrolled at that same dose level. Dose escalation will continue until at least two of the three to six patients treated at a dose level experience a DLT. The next lower dose will then be considered the MTD. Alternatively, if the dose between the MTD and the maximally delivered dose is significant (such as 100%), then a more modestly de-escalated dose may be explored (e.g., 20 to 50%).

The three patients initially enrolled at each dose level will be used for dose escalation decisions. Up to three additional patients may be enrolled at any previously evaluated dose level in order to further characterize inter-patient PK variability. Evaluation of the next dose level and expanded evaluation of the previously evaluated dose may occur simultaneously; however, enrollment into these cohorts will be sequential. The first three eligible patients will be enrolled into the dose escalation cohort. Once the dose escalation cohort has been filled, up to three additional patients may be enrolled at a previously evaluated dose level if additional PK assessment is warranted.

Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein investigators and the sponsor's medical monitor will review patient data, including but not limited to demographics, PK results, oral rucaparib dosing, concomitant medications, hematology and serum chemistry, and AEs, and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe.

RP2D Selection and Expansion

The RP2D for evaluation in Part 2 (Phase II portion) will be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data. The RP2D may or may not be the same as the MTD identified in Part 1. For example, if the MTD is not reached, if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RP2D may be a different, although not higher, dose than the MTD.

Once the RP2D has been provisionally established, up to 15 additional patients with a solid tumor and a deleterious *gBRCA* mutation will be enrolled and treated at that dose in order to further characterize safety, tolerability, and PK, and confirm that this is the optimal dose to evaluate in Part 2. Since the RP2D may have been selected based on evaluation of as few as 3 patients, there is low certainty that the RP2D has a toxicity rate that is <33%. Enrolling up to an additional 15 patients will increase the certainty that the Phase II component of the study is evaluated at a dose with a DLT rate <33%. If ≥33% of patients at the RP2D experience a DLT, then enrollment into the RP2D Expansion cohort will stop and a lower dose will be explored.

The dose of 600 mg BID rucaparib has been selected as the recommended dose for Phase II and Phase III studies based on the overall safety & tolerability, PK, and clinical activity profile. The MTD was not reached in Part 1 (See Section 3.2.2).

Food-Effect PK Evaluation

The effect of food on oral rucaparib PK will be assessed prior to, and during, Cycle 1 in three patients. Food effect PK analysis will be performed once evaluation of Cohort 1 (40 mg) is completed, and will be conducted either at the next escalated dose, or as expanded PK evaluation of the 40 mg dose level. The dose level for evaluation will be established at the safety teleconference call for Cohort 1. Food-effect PK may be conducted in additional cohorts in Part 1 if results from prior cohort(s) warrant expanded evaluation.

Effect on QTc

ECGs will be collected in all patients enrolled in Part 1, including those in the RP2D Expansion cohort, in order to assess the effect of oral rucaparib on QTc. ECGs in Part 1 will be performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory. The Sponsor will allow local ECG testing once sufficient centrally obtained data has been collected.

Metabolite Profiling

The first three patients enrolled into the RP2D Expansion cohort will have additional blood samples collected on Day 1 (predose sample only) and Day 15 of Cycle 1 for assessment of plasma metabolites.

Tumor Mutation Status

Optional formalin-fixed paraffin-embedded (FFPE) archival and/or fresh tumor tissue samples collected at screening, and at disease progression/treatment discontinuation in Part 1 will be analyzed for changes in mutation status.

Treatment-Extension Period

Upon completion of Cycle 1 (Safety and PK Assessment Period), Part 1 patients may participate in an optional Treatment-Extension Period, which begins on Day 1 of Cycle 2. Oral rucaparib will be administered daily during this period (21 day cycles) until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

5.1.3 Part 2 (Phase II Portion in Patients with BRCA-Mutant Ovarian Cancer)

Enrollment into Part 2 (Phase II portion) will begin when all patients enrolled into the RP2D Expansion cohort have completed two cycles of treatment, or have discontinued from the study prior to completing two cycles of treatment.

Patients enrolled into Part 2 will be assessed for tolerability and efficacy. Patients will be treated until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

The Part 2A study will use a Simon 2-stage design to evaluate the efficacy of rucaparib. Initially 21 patients will be treated in Stage 1; if two or more patients in Stage 1 have an objective response (complete response [CR] or partial response [PR]) then the remaining 20 patients will be treated in Stage 2. If fewer than two patients in Stage 1 have an objective response, then no further patients will be enrolled.

The criteria for Stage 1 success were met in April 2014, and Stage 2 enrollment of 41 patients was completed in April 2015.

An additional cohort of 40 *BRCA* mutant OC patients will be evaluated in Part 2B. Enrollment of this portion of the study will begin after enrollment of Part 2A has been completed. Part 2B will run concurrently with Part 3.

5.1.4 Part 3 (Phase II PK Portion in Patients with any Advanced Solid Tumor)

Part 3 will enroll in parallel with Part 2. Part 3 is an initial randomized, single dose, two treatment, two period, crossover design, to explore food effect; with subsequent continuous BID dosing. It is estimated that enrolling approximately 20 evaluable patients will provide sufficient

data for PK analysis. A randomization scheme using blocks of four will assign patients to either a sequence of fasted at Day -7 and fed at Day 1 or a sequence with fed at Day -7 and fasted at Day 1.

After Day 1 patients will continue with BID continuous dosing and will also be assessed for safety and tolerability. Additional detailed PK to assess steady state will be done at Day 15 of Cycle 1. Patients will be treated until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

Food-Effect PK Evaluation

All patients enrolled into Part 3 will have plasma samples drawn in order to evaluate the PK profile of a single dose of 600 mg administered as 300 mg tablets in the fed versus fasted state.

5.1.5 End-of-Treatment and Follow-Up (Part 1, Part 2, and Part 3)

All patients should return to the clinic for end-of-treatment assessments upon discontinuation of rucaparib and for follow-up of AEs at 28 (±3) days after the last dose of oral rucaparib has been administered. During Parts 1 to 3, AEs will be assessed from the time of informed consent through 28 days after the last dose. Part 2B patients will be followed for survival, subsequent treatments, and secondary malignancy monitoring every 12 weeks [±7 days].

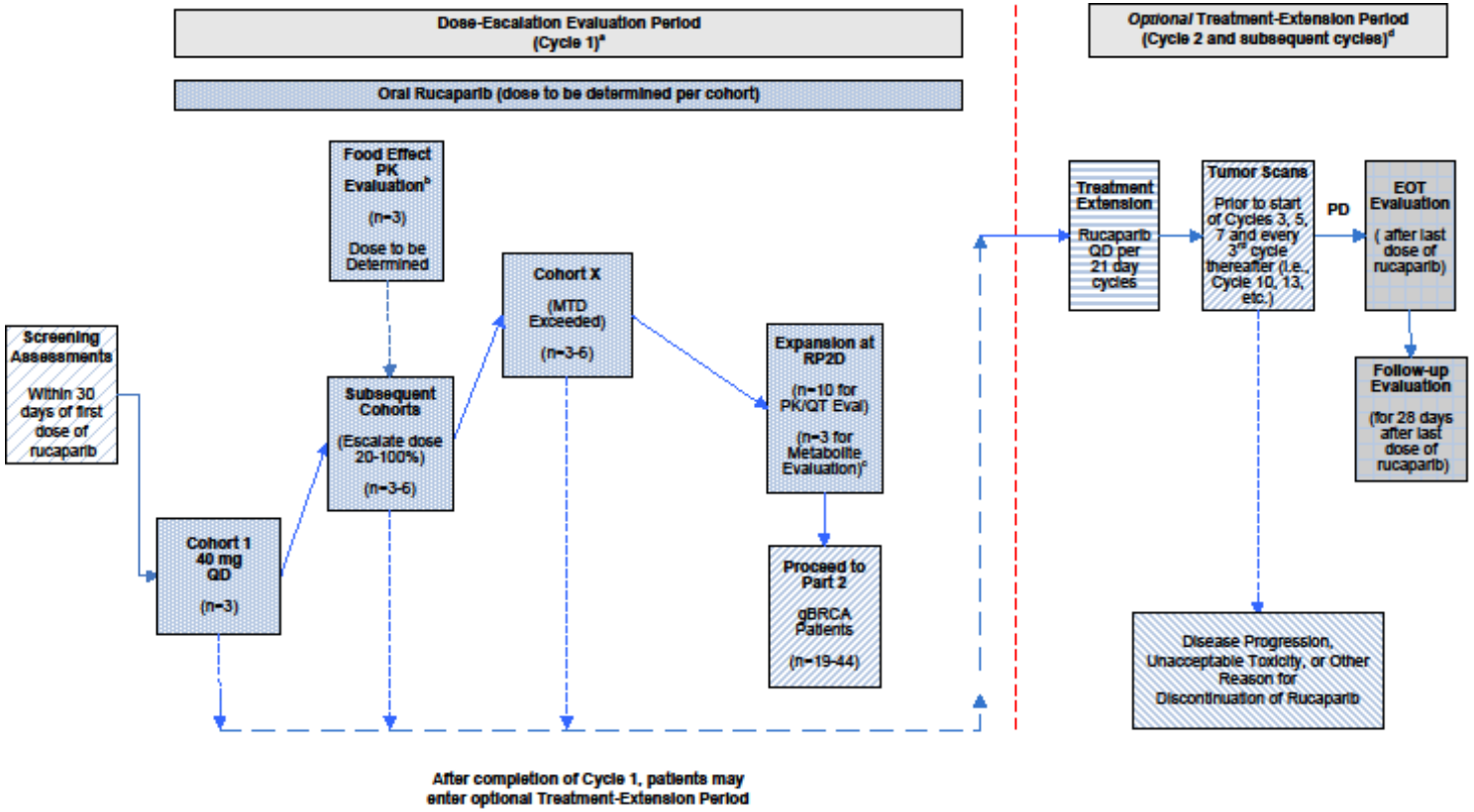
5.1.6 End of Study

The trial will be completed when all enrolled patients have experienced PD, or have discontinued the study due to another reason.

5.2 Study Schema

The study schema in Figure 2, Figure 3, and Figure 4 summarize the treatment designs for Part 1, Part 2, and Part 3 of the study.

Figure 2. Study Schema Part 1



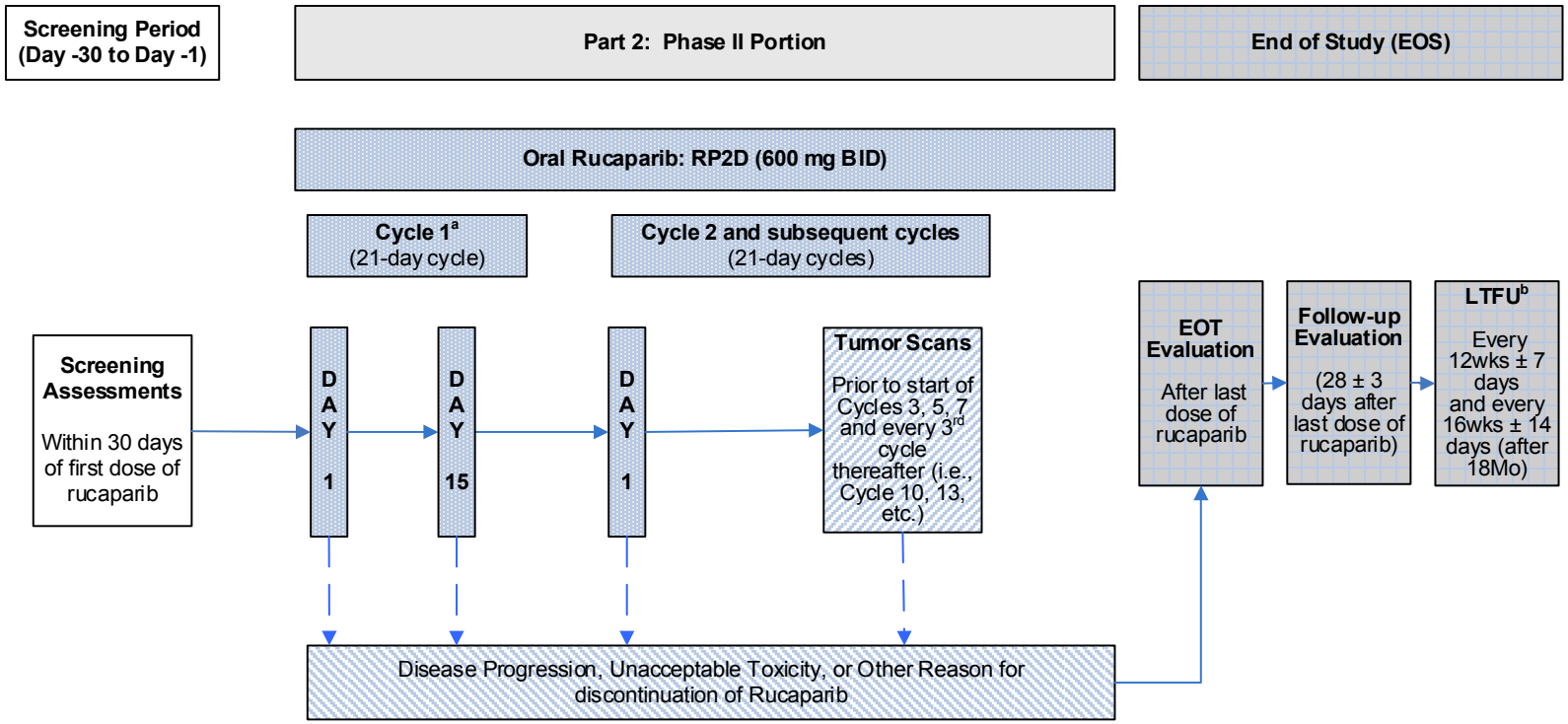
[a] The Dose-Escalation Evaluation Period comprises one cycle of treatment (21 day cycle) within each cohort, with the exception of the RP2D Expansion cohort (anticipated to receive at least two cycles of treatment).

[b] The food-effect PK evaluation will be conducted in three patients (see Table 10 and Table 12) at a dose level to be determined once the Cohort 1 evaluation is completed.

[c] Once RP2D is established, up to 15 additional patients will be treated at the RP2D and undergo further PK and QT evaluations; in addition, 3 of these patients will have additional blood collection for metabolite profiling (see Table 9 and Table 12).

[d] After completing Cycle 1, patients may enter an optional Treatment-Extension Period.

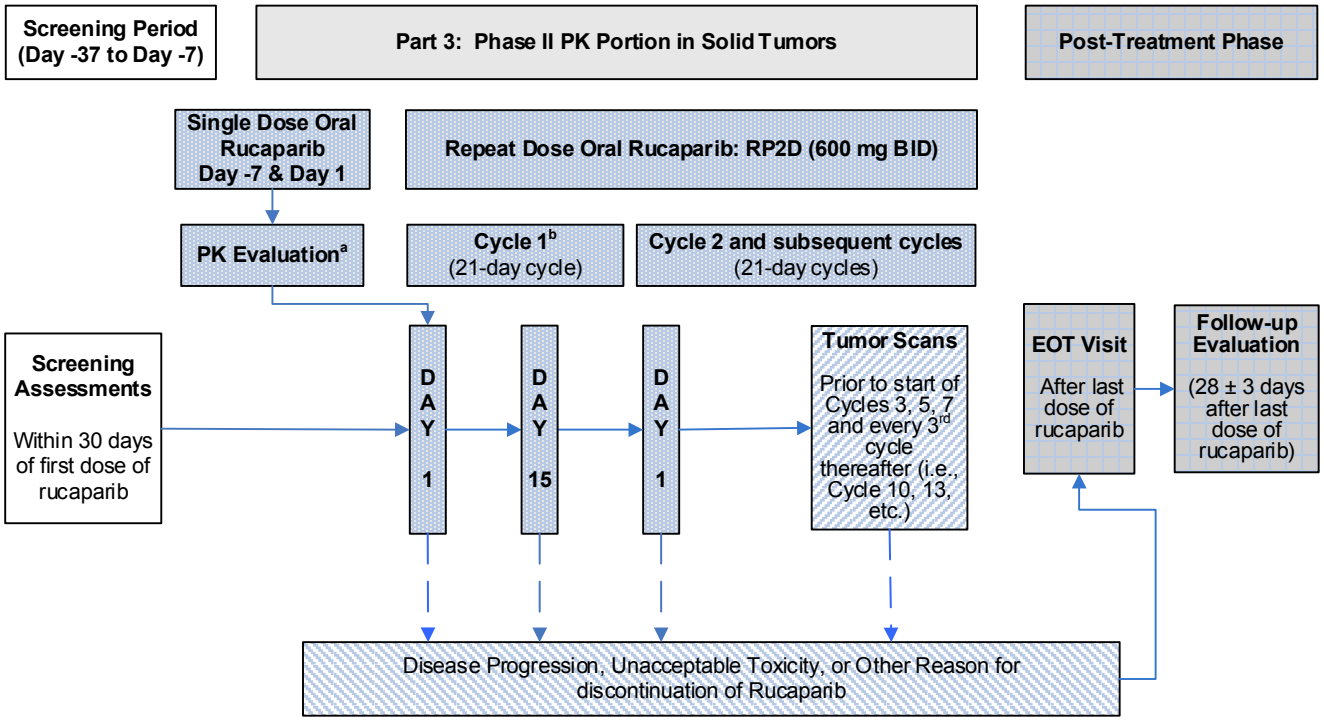
Figure 3. Study Schema Part 2



[a] At Cycle 1 only, patients will undergo assessments on Days 1 and 15.

[b] Part 2B only

Figure 4. Study Schema Part 3



[a] The food-effect PK evaluation will be conducted in approximately 20 patients (see Table 13 and Table 14).
[b] At Cycle 1 only, patients will undergo assessments on Days 1 and 15.

6 STUDY POPULATION

6.1 Number of Patients and Sites

In Part 1 (Phase I portion), approximately 50 – 60 patients with locally advanced or metastatic solid tumors, inclusive of lymphoma, who have progressed on standard treatment will be enrolled at up to six study sites. Patients enrolled into the RP2D Expansion Cohort must also have a documented deleterious *gBRCA* mutation.

In Part 2A (Phase II portion), up to a total of 41 evaluable patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *gBRCA* mutation, will be enrolled from approximately 20 study sites.

In Part 2B (Phase II portion), up to a total of 40 evaluable patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with evidence of a deleterious *BRCA* mutation (germline or somatic), will be enrolled from approximately 20 study sites.

In Part 3 (Phase II portion), approximately 20 evaluable patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a *BRCA* mutation (germline or somatic), will be enrolled from approximately 8 study sites. Evaluable patients are defined as patients who have complete PK analysis data in both periods for the initial randomized cross-over design exploring the food effect during assessment Day -7 and Day 1.

6.2 Inclusion Criteria

All patients enrolling into **Part 1 (Phase I portion), Part 2 or Part 3 (Phase II portions)** must meet <u>all</u> of the following inclusion criteria:

1. Understand and voluntarily sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Be ≥18 years of age at the time the informed consent form is signed
3. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
4. Have a life expectancy of at least 3 months
5. Have adequate organ function, confirmed by the following laboratory values obtained ≤14 days prior to the first dose of rucaparib:

   <u>Bone Marrow Function</u>

   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelets $>100 \times 10^9$/L
   - Hemoglobin ≥9 g/dL

Hepatic Function

- Aspartate aminotransferase (AST) and ALT ≤3 × upper limit of normal (ULN); if liver metastases, then ≤5 × ULN
- Bilirubin ≤1.5 × ULN (<2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome)
- Serum albumin ≥30 g/L (3.0 g/dL) ***(Part 2B only)***

Renal Function

- Serum creatinine ≤1.5 × ULN

Patients enrolling into **Part 1 (Phase I portion)** must also meet the following inclusion criteria:

6. (a) Have a histologically or cytologically confirmed solid tumor (lymphoma is included in this category) that is locally recurrent or metastatic and has progressed on standard treatment.
7. (a) Have left ventricular ejection fraction (LVEF) > lower level of normal (LLN) as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan evaluation using local institutional standard
8. (a) Be willing and able to eat a high-fat breakfast on Day 1 of the study ***(Note: only applicable for patients being screened for enrollment into a food-effect PK cohort)***
9. (a) Have a deleterious *gBRCA* mutation ***(Note: only applicable for patients being screened for enrollment into the RP2D Expansion cohort)***

All patients enrolling into **Part 2 (Phase II portion in OC patients)** must also meet the following inclusion criteria:

6. (d) Have a known deleterious *BRCA* mutation (germline or somatic), as determined by a local laboratory that has received an international or country-specific quality standards certification
7. (d) Have evidence of measurable disease as defined by RECIST v1.1
8. (d) Have sufficient archival FFPE tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable

    - Archival tissue from the most recently collected biopsy or debulking surgery should be provided, if available. Otherwise, the next oldest tissue collected should be reviewed until a suitable sample can be provided (at least 20% tumor content with a minimum of 80% nucleated cellular content)

Additional inclusion criteria for patients into **Part 2A (Phase II portion in OC**) include:

9. (b) Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer

    - For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid upon re-review by local pathology

10. (b) Have received at least two, but no more than four, prior chemotherapy regimens and have relapsed as confirmed by radiologic assessment
    a. Last treatment received must have been platinum-based regimen to which patient must have been sensitive (i.e., disease progression occurred at least 6 months after last dose of platinum was administered)
    b. A maximum of one non-platinum regimen may have been administered. For patients who received four prior regimens, one regimen must have been a non-platinum
    c. Prior continuous or switch maintenance treatment is permitted (hormonal treatment may be permitted following the last platinum regimen with advance approval from the sponsor)

Additional inclusion criteria for patients into **Part 2B (Phase II portion in OC)** include:

9. (d) Have a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.
10. (d)Have received at least three, but no more than four, prior chemotherapy regimens and have relapsed disease confirmed by radiologic assessment
    - Hormonal agents (e.g., tamoxifen, letrozole, etc), anti-angiogenic agents (e.g., bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc), and other non-chemotherapy agents administered as single agent treatment will not be counted as a chemotherapy regimen for the purpose of determining patient eligibility
    - Agents administered in the maintenance setting will not be counted as a separate regimen
11. (d) Have a documented treatment-free interval (TFI) of ≥6 months following the first chemotherapy regimen received. (TFI is determined from the last dose administered as part of primary treatment regimen and not from the last dose of any agent administered in the maintenance setting)

Patients enrolling into **Part 3 (Phase II PK portion in patients with any advanced solid tumor)** must also meet the following inclusion criteria:

6. (c) Have an advanced solid tumor (inclusive of lymphoma)
7. (c) Have a known deleterious *BRCA* mutation (*gBRCA* or somatic *BRCA* [*sBRCA]*), as determined by a local laboratory that has received an international or country-specific, quality standards certification
8. (c) Have evidence of measurable disease as defined by RECIST Version 1.1
9. (c) Be willing and able to fast, and to eat a high-fat breakfast on Day -7 or Day 1 of the study
10. (c) Have sufficient archival FFPE tumor tissue available for planned analyses; cytospin blocks from ascites are not acceptable

- Archival tissue from the most recently collected biopsy or debulking surgery should be provided, if available. Otherwise, the next oldest tissue collected should be reviewed until a suitable sample can be provided (at least 20% tumor content with a minimum of 80% nucleated cellular content)

6.3 Exclusion Criteria

Patients enrolling into **Part 1 (Phase I portion), Part 2 or Part 3 (Phase II portions)** will be excluded from participation if any of the following criteria apply:

1. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which she/he may be (but not necessarily) currently receiving treatment
   - Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed >6 months prior and/or any bone marrow transplant (BMT) >2 years prior to first dose of rucaparib
2. Prior treatment with any PARP inhibitor (*Part 1 and Part 2*). Part 3 patients are permitted to have had previous PARPi, if the following conditions are met:
   - PARPi was not the most recent treatment, and
   - PARPi was discontinued >6 months before first planned dose of rucaparib
   - In all study parts, patients who previously received iniparib are eligible
3. Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks
4. (Criterion removed in Amend 5).
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
6. Received 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 adverse effects from such treatment > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen may be permitted with prior advanced approval from Sponsor)
7. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib
8. Administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first scheduled dose of rucaparib

9. 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
10. Females who are pregnant or breastfeeding
11. For fertile patients (female able to become pregnant or male able to father a child), refusal to use effective contraception during the period of the trial and for 6 months after the last dose of oral rucaparib
12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse; psychiatric disturbance; or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
13. 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
14. (Criterion removed in Amend 5).

Patients enrolling into **Part 1 (Phase I portion)** of the study will also be excluded from participation if any of the following criteria apply:

15. Family history of long QT syndrome
16. Implantable pacemaker or implantable cardioverter defibrillator, and
17. Requires treatment with any medication known to produce QT prolongation, with the exception of necessary antiemetic medications (see Appendix C)

Patients enrolling into **Part 2B (Phase II OC portion)** will also be excluded from participation if any of the following criteria apply:

18. Hospitalization for bowel obstruction within 3 months prior to enrollment

6.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients are considered to be of childbearing potential unless 1 of the following applies:

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

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

Female patients of childbearing potential must have a negative serum pregnancy ≤ 3 days prior to administration of the first dose of oral rucaparib. In addition, 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 will be performed at the End-of-Treatment Visit. Pregnancy testing will be conducted locally.

Female patients of childbearing potential and male patients of reproductive potential must practice a highly effective method (failure rate < 1% per year) of contraception during treatment and for 6 months following the last dose of rucaparib. Highly effective contraception includes:

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

It is recommended that opposite sex partners of patients use a highly effective contraception method as specified above during and for 6 months following the patient's treatment.

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

6.5 Waivers of Inclusion/Exclusion Criteria

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

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Investigational Product

Rucaparib camsylate (also known as CO-338; previously known as PF-01367338-BW) 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.

Drug Name:	Rucaparib camsylate (CO-338)
INN:	Rucaparib
Formulation:	Tablet; film coated; 40 mg – white, 60 mg – white, 120 mg – salmon, 200 mg – blue, 300 mg – yellow
How Supplied:	40, 60, 120, 200 and/or 300 mg (as free base) strength in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive one or more strengths.
Storage Conditions:	15–30 °C

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

7.2 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive oral rucaparib.

7.3 Preparation and Administration of Protocol-Specified Treatment

The investigator or designee will be responsible for distributing the appropriate strength(s) of oral rucaparib tablets to all patients. Study sites should follow local guidelines for the handling of oral cytotoxic drugs.

With the exception of Day -7 and Day 1 of the food effect PK portions of the study in Part 1 and Part 3, patients may take rucaparib on an empty stomach or with food. Each dose should be taken with 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole. Patients on a BID dosing schedule should take rucaparib doses as close to 12 hours apart as possible. In the event TID dosing is explored, patients on this schedule should take doses approximately 8 hours apart. Administration conditions may be revised based on PK results obtained in Part 1 or Part 3.

Part 1 (Phase I Portion)

In each cohort, patients will ingest rucaparib once, twice, or three times a day through Day 21 of Cycle 1. Patients who enter the optional Treatment-Extension Period will continue treatment with rucaparib starting on Day 1 of Cycle 2.

Part 2 and Part 3 (Phase II Portions)

Patients enrolled in Part 2 or Part 3 will ingest oral rucaparib (21 day cycles) at 600 mg BID, as determined in Part 1.

Part 2A patients will receive 120 mg tablets. Following the assessment of higher dose strength tablets in Part 3, Part 2A patients may be transferred to 200/300 mg tablets if supply of 120 mg tablets is exhausted. Part 2B and Part 3 patients will receive 200/300 mg tablets only.

Where applicable, changing from 120 mg to 200/300 mg strength tablets should be made according to Table 3 below:

Table 3. Comparison of Dose Levels when Switching to 200/300 mg Strength Tablets from 120 mg Tablets

	Dose with 120 mg	Dose with 200/300 mg
Starting Dose Level	**600 mg BID**	
Dose Level -1	480 mg BID	500 mg BID
Dose Level -2	360 mg BID	400 mg BID
Dose Level -3	240 mg BID	300 mg BID

If a patient misses a dose (i.e., does not take it within 4 h of the scheduled time on a BID schedule), she should resume taking rucaparib with her next scheduled dose. Missed or vomited doses will not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken on a patient diary, and will be instructed to bring their rucaparib tablets and diary to the next scheduled visit for reconciliation by site personnel.

7.3.1 Dietary Restrictions

Patients should be instructed to limit their coffee intake to one 8 oz (240 mL) cup of black coffee (no cream or sugar) and to not consume alcohol, tea, chocolate, or cola beverages within 2 h prior to collection of PK samples on days where PK sampling is extensive (i.e., pre- and post-rucaparib administration). This restriction does not apply on days when only a predose trough level PK sample is collected.

7.3.2 Fed and Fasted Requirements for Food-Effect PK Analysis

Fasted Condition

Following an overnight fast of at least 10 h, and following performance of all required predose assessments, patients will ingest oral rucaparib with 8 oz (240 mL) of room temperature water.

No food will be allowed for at least 4 h postdose. No water will be allowed for at least 2 h postdose.

Fed Condition

Following an overnight fast of at least 10 h, and following performance of all required predose assessments, patients will consume a high-fat (approximately 50% of total caloric content), high-calorie (approximately 800–1000 calories total) breakfast meal containing approximately 500 to 600 calories from fat, approximately 250 calories from carbohydrates, and approximately 150 calories from protein, in the clinic. Patients must begin eating the meal 30 (±5) min prior to the planned administration of oral rucaparib. Patients should eat this meal in 30 min or less; however, oral rucaparib should be administered 30 min after the start of the meal, regardless of whether the meal was completed or not. Patients will ingest oral rucaparib with 8 oz (240 mL) of room temperature water. No food will be allowed for at least 4 h postdose. No water will be allowed for at least 2 h postdose.

The breakfast meal will be provided by the clinical site or patient. A list of appropriate breakfast meals will be provided to clinical sites and patients by the sponsor. An example test meal would be two eggs fried in butter, two strips of bacon (or ham or cheese of similar caloric content), two slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz (240 mL) of whole-fat milk. A different breakfast meal to suit specific dietary requirements may be substituted by the clinical site or patient, provided that it has a similar amount of calories and protein, and carbohydrate and fat content. The nutrient content of the proposed meal must be calculated and submitted to the sponsor (or designee) for review and approval at least 3 days in advance of the patient's scheduled fed day.

7.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

7.4.1 Part 1 (Phase I Portion)

7.4.1.1 Dose Escalation

In Cohort 1, three patients will be enrolled initially at a starting dose of 40 mg oral rucaparib. Enrollment, treatment, and evaluation of each patient can occur in parallel. There is no period of observation between patients enrolled into a dose-escalation cohort. The occurrence of DLTs (Section 7.4.1.3) will determine whether the dose level will be escalated in subsequent cohorts. The dose-escalation decision rules are summarized in Table 4.

Table 4. Dose-Escalation Decision Rules

Number of Patients with DLT at a Dose Level	Decision
0 of 3	Escalate dose as specified in Table 5 and evaluate in 3 subsequent patients.

Table 4. Dose-Escalation Decision Rules	
Number of Patients with DLT at a Dose Level	**Decision**
1 of 3	Enroll 3 additional patients at this dose level. Then: • If 0 of these 3 additional patients has a DLT, proceed to the next dose level. Escalate dose as specified in Table 5 and evaluate in 3 subsequent patients. • If 1 or more of these additional patients has a DLT, then dose escalation is stopped and this dose is declared the maximum administered dose. Three additional patients will be enrolled at the previously evaluated dose level if only 3 patients were treated at that dose previously.
≥2 of 3	The MTD has been exceeded. Dose escalation will stop and this dose level will be declared the maximum administered dose. Evaluate 3 additional patients at the prior dose level if only 3 were treated at that dose previously. (An interim de-escalated dose may be explored if the increment between MTD and maximally administered dose was >50%).
1 of 6	Proceed to next dose level (if not evaluated previously) and evaluate 3 patients. Escalate dose as specified in Table 5 and evaluate in 3 subsequent patients.
≤1 out of 6 at the Highest Dose Below the Maximum Administered Dose	This is the MTD.
≥2 of 6	The MTD has been exceeded. Dose escalation will stop and this dose level will be declared the maximum administered dose. Evaluate 3 additional patients at the prior dose level if only 3 were treated at that dose previously. (An interim de-escalated dose may be explored if the increment between MTD and maximally administered dose was >50%).

Dose escalation based on DLTs observed, overall tolerability, and PK results will proceed as specified in Table 5 until an MTD is determined. Dose escalation steps above 360 mg BID will be agreed upon between the Investigators and Sponsor's Medical Monitor, but will not exceed 100%. In the event TID dosing is explored, the starting dose will be determined based on safety and PK observed in prior BID cohorts and will be agreed upon between the Investigators and Sponsor's Medical Monitor. Additional subjects may be treated at any previously evaluated dose level in a treatment schedule in order to better characterize safety and PK/PD parameters. Intermediate or lower dose levels may also be explored for determining the RP2D following discussion and agreement between the Investigators and the Sponsor's Medical Monitor.

Table 5. Dose-Escalation Plan

Dose and Frequency	Total Daily Dose	Increase in Total Dose (Actual or Planned)
40 mg QD	40 mg	-----
80 mg QD	80 mg	100% (Actual)
160 mg QD	160 mg	100% (Actual)
300 mg QD	300 mg	88% (Actual)
500 mg QD	500 mg	67% (Actual)
240 mg BID	480 mg	50% (Actual)
360 mg BID	720 mg	50% (Actual)
480 mg BID	960 mg	33% (Actual)
600 mg BID	1200 mg	25% (Actual)
840 mg BID	1680 mg	40% (Actual)

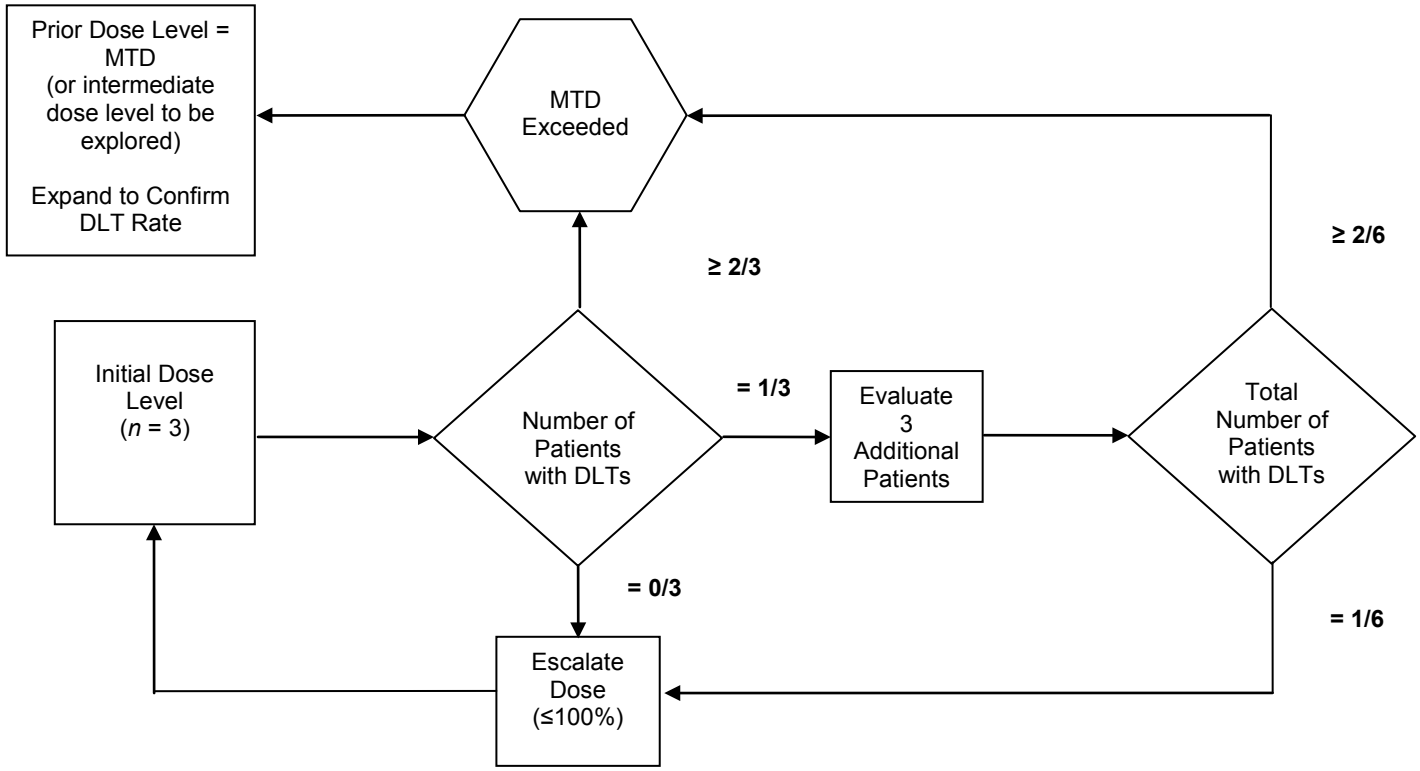
7.4.1.2 Maximum Tolerated Dose

The MTD is defined as the maximum daily oral dose at which <33% of patients experience a DLT during Cycle 1 (Safety and PK Assessment Period). If a DLT is observed in one of three patients, then three additional patients will be enrolled at that same dose level. Dose escalation will continue until at least two of the three to six patients treated at a dose level experience a DLT. The next lower dose will then be considered the MTD. Alternatively, if the dose between the MTD and the maximally delivered dose is significant (such as 100%), then a more modestly de-escalated dose may be explored (e.g., 20 to 50%).

7.4.1.3 Dose-Escalation Design

The dose-escalation design for this study is presented graphically in Figure 5 below.

Figure 5. Dose-Escalation Design



7.4.1.4 Dose-Limiting Toxicity

DLTs in Part 1 will be defined as any of the following events that occur during Cycle 1 (Safety and PK Assessment Period) and are assessed by the investigator as related to rucaparib. Where applicable, events will be classified according to the NCI CTCAE.[2]

- ANC $<0.5 \times 10^9$/L >5 days duration or febrile neutropenia (i.e., fever > 38.3°C with ANC $<1.0 \times 10^9$/L)
- Platelets $<25 \times 10^9$/L or platelets $<50 \times 10^9$/L with bleeding requiring a platelet transfusion
- Grade 4 anemia (i.e., life-threatening consequences; urgent intervention indicated)
- Any nonhematological AE CTCAE Grade 3 or greater (except alopecia and nausea, vomiting, and diarrhea if well-controlled by systemic medication)

7.4.1.5 Definition of DLT-Evaluable Patient

In order to be considered evaluable for dose-escalation decisions, a patient in Part 1 must have:

- Received at least 17 complete days of dosing, and have completed Cycle 1, Day 21 without a DLT, or
- Have experienced a DLT in Cycle 1

If a patient withdraws from the study without having met either of these criteria, then an additional patient will be enrolled in that cohort.

7.4.1.6 In the Event of Toxicity at Lowest Dose Level

In the event 240 mg BID rucaparib exceeds the MTD, a dose of 180 mg (or lower) BID rucaparib may be explored. In the event TID dosing is explored and the starting dose of rucaparib on that schedule exceeds the MTD, a lower dose of rucaparib may be explored.

7.4.1.7 Recommended Phase II Dose

The RP2D for evaluation in Part 2 and Part 3 will be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data. The RP2D may or may not be the same as the MTD identified in Part 1 of the study. For example, if the MTD is not reached, if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RP2D may be a different, although not a higher, dose than the MTD.

Note: The dose of 600 mg BID rucaparib was selected as the recommended dose for Part 2 and Part 3 based on the overall safety and tolerability, PK, and clinical activity profile (See Section 3.2.2). The MTD was not reached in Part 1.

7.4.1.8 Dose Modification Criteria

In Part 1, no dose reduction is permitted in Cycle 1. After Cycle 1, dose reductions are permitted as indicated in Table 6.

If a patient in Part 1 is confirmed to have experienced a DLT in Cycle 1, then the investigator may do either of the following:

- Continue treating the patient at the next lower dose level evaluated (oral rucaparib is not to be reduced below 40 mg) if the investigator expects clinical benefit from further treatment with rucaparib, the toxicity is manageable, and the investigator and the sponsor's medical monitor (or designee) agree. A patient who receives a modified dose will be evaluated for safety at that dose level, but will not be counted towards the number of patients with DLTs at that dose level.
- Discontinue the patient from rucaparib treatment and the study.

During the optional Treatment-Extension Period, the dose of oral rucaparib may be reduced to the next lower dose level evaluated if any of the following are observed:

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

7.4.1.8.1 Management of Rucaparib Treatment-emergent ALT/AST Elevations

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

- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:

  – Monitor liver function tests weekly until resolution to ≤ Grade 2.

  – Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN 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.

Treatment with rucaparib should be held until the toxicity resolves to ≤Grade 2. Dosing may then be resumed at either the same dose or the next lower dose level evaluated, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event. If the patient continues to experience toxicity, a second and third dose reduction to a previously evaluated lower dose are permitted. Up to three dose reduction steps are allowed. If a patient continues to experience toxicity after three dose reduction steps, or if dosing with rucaparib is interrupted for >14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor.

Dose reduction levels from doses that may be administered during the study are presented in Table 6, Table 7, and Table 8.

Table 6. Example Dose Reduction Steps

Possible Dose Levels	First Adjustment	Second Adjustment*
40 mg QD	NA	NA
80 mg QD	40 mg QD	NA
160 mg QD	80 mg QD	40 mg QD
300 mg QD	160 mg QD	80 mg QD
500 mg QD	300 mg QD	160 mg QD
240 mg BID	180 mg BID	To be agreed upon between Sponsor's Medical Monitor and Investigator
360 mg BID	240 mg BID	To be agreed upon between Sponsor's Medical Monitor and Investigator
Additional Dose Level(s) BID	To be agreed upon between Sponsor's Medical Monitor and Investigator	To be agreed upon between Sponsor's Medical Monitor and Investigator
TID	In the event TID dosing is explored, dose adjustments will be agreed upon between the Sponsor's Medical Monitor and the Investigator.	In the event TID dosing is explored, dose adjustments will be agreed upon between the Sponsor's Medical Monitor and the Investigator.

NA=Not applicable.
*Additional Dose reduction allowed as agreed upon between Sponsor's Medical Monitor and Investigator

7.4.1.9 Intrapatient Dose Escalation

Intrapatient dose escalation in Part 1 of the study will be permitted after a subject completes at least 2 cycles of treatment at their initial dose level without experiencing significant drug-related toxicity, provided the dose level to which the patient will escalate has been evaluated and deemed tolerable at the time of the proposed dose increase, and represents ≤100% increase in total dose. The dose may be increased at the beginning of the next cycle. There is no limit to the

number of dose escalation steps permitted for an individual patient provided all criteria are met. All dose escalation steps must be approved by the Sponsor's Medical Monitor.

7.4.1.10 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥75.0 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient)

7.4.2 Part 2 and Part 3 (Phase II Portion)

7.4.2.1 Starting Dose

The RP2D identified in Part 1 (Phase I portion) will be the starting dose for patients enrolled into Part 2 and Part 3 (Phase II portion). The dose of 600 mg BID was selected as the recommended dose for Part 2 and Part 3 based on the overall safety & tolerability, PK, and clinical activity profile. Refer to Section 3.2.2 for more detail.

7.4.2.2 Dose Modification Criteria

Patients in Part 2A using 120 mg tablets should have their dose of oral rucaparib modified as needed (see Section 7.4.1.8 and Table 7).

Table 7. Dose Reduction Steps in Part 2A (Phase II in Patients with OC) using 120 mg tablets

Starting Dose	600 mg BID
Dose Level -1	480 mg BID
Dose Level -2	360 mg BID
Dose Level -3	240 mg BID

Patients in Part 2A, Part 2B, and Part 3 using 200/300 mg tablets should have their dose of oral rucaparib modified as needed (see Section 7.4.1.8 and Table 8).

Table 8. Dose Reduction Steps in Part 2A and Part 2B (Phase II in Patients with OC) and Part 3 (Phase II in Patients with any Advanced Solid Tumor) using 300 and 200 mg tablets	
Starting Dose	**600 mg BID**
Dose Level -1	500 mg BID
Dose Level -2	400 mg BID
Dose Level -3	300 mg BID
Dose Level -4	200 mg BID*
*200 mg dose level is only permitted following discussion with the Sponsor	

If a patient was required to reduce their dose level due to a toxicity, and the toxicity subsequently resolved, the dose may be re-escalated at the discretion of the investigator.

7.4.3 In the Event of Torsade de Pointes

In the event of ECG result or adverse event(s) suggestive of "torsade de pointes," the following procedures are recommended:

1. Hold rucaparib.
2. Check for hypokalemia, hypomagnesemia, and hypocalcemia.
3. Check cardiac enzymes. Rule out myocardial ischemia, especially in patients without QT prolongation.
4. Perform chest radiographs and ECHO to rule out structural heart disease, if any clinical suggestion is present.
5. Order other tests as appropriate, depending on the etiological factors being considered.
6. Administer treatment (if required) appropriate to diagnosis.
7. Submit SAE Report, if applicable.
8. Resume treatment with rucaparib if appropriate, or discontinue treatment permanently and schedule an end-of-study visit.

7.4.4 Treatment Beyond Progression

If the patient has met the criteria for radiologic progression by RECIST, but the patient is still receiving benefit from rucaparib (e.g., patient has mixed radiologic response or is continuing to have symptomatic benefit) according to the Investigator, then continuation of treatment will be considered. In such cases, the decision to continue will be made jointly between the Investigator and the Sponsor, and must be documented prior to continuing treatment with rucaparib. Patients will continue to have all protocol-required assessments specified in Table 9, Table 10, Table 11, and Table 13.

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of oral rucaparib shipments/receipts, administration, and drug reconciliation. The site is responsible for the return or destruction of oral rucaparib as required. A drug management system will manage oral rucaparib inventory at all sites. The system will be required to manage study treatment requests and shipments.

Any oral rucaparib accidentally or deliberately destroyed must be accounted for. All bottles must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of cytotoxic drugs. Unused bottles should be destroyed locally. If destruction at 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 bottles of oral rucaparib shipped, destroyed, and returned must be reconciled.

7.6 Blinding/Masking of Treatment

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

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific diary (paper or electronic) provided by the sponsor (or designee). Study site personnel will provide instructions regarding the scheduled daily doses and the number of tablets to be taken each day. Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days. Patients (or legally authorized representative) will be asked to record dosing information for oral rucaparib taken at home in the diary and to bring the diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel. In the event paper diary cards are utilized, study site personnel will record compliance information on the case report form (CRF) and retain the diary card in the patient's medical record.

8 PRIOR AND CONCOMITANT THERAPIES

Patients who have received prior treatment with a PARP inhibitor, including intravenous and oral rucaparib, are not eligible to participate in Part 1 or Part 2 of this study. Patients in Part 3 are allowed to receive prior treatment with a PARP inhibitor provided that it was not the most recent treatment and that the PARPi was discontinued at least 6 months before the first planned dose of rucaparib. Patients having received prior treatment with iniparib are eligible.

During the study, supportive care (e.g., antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. For patients undergoing ECG assessments in Part 1, medications known to produce QT prolongation should not be used, with the exception of necessary antiemetic medications. A list of prohibited medications and antiemetic medications requiring additional ECG monitoring is provided in Appendix C. These restrictions do not apply to Part 2 or Part 3.

All procedures performed (e.g., thoracentesis, etc.) and medications used during the study must be documented on the electronic case report form (eCRF).

8.1 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment [except corticosteroids and megestrol acetate], antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, matrix metalloprotease inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study with the exception of ongoing hormonal treatment for prior breast cancer. Prior treatment with such therapies must have been completed >14 days prior to the first scheduled dose or oral rucaparib.

8.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Prophylactic use of these agents is not permitted.

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.3 Antiemetics

Some antiemetics commonly administered to the patient population in this study are associated with QT prolongation; these should be avoided (from the time of informed consent until the time of the last ECG) whenever possible for all patients enrolled into Part 1 of the study. Preferable antiemetics in Part 1 include phenothiazines and corticosteroids. Administration of prophylactic antiemetics is prohibited during Cycle 1 of treatment for patients in Part 1 to ensure patients are fully evaluable for dose-limiting toxicity evaluation during this cycle of treatment. There are no restrictions on antiemetics in Part 2 or Part 3.

Patients in Part 1 receiving antiemetic medications known to produce QT prolongation will require additional ECG measurements at estimated T_{max}. ECGs should be performed approximately 2, 4, and 6-7 hours after dosing with rucaparib when the patient begins treatment with the antiemetic and again at the same timepoints 1 to 2 weeks later.

8.4 CYP450 Isoenzyme Inhibitors and Inducers

Based on results of in vitro CYP interaction studies (Section 3.2.1.1), caution should be used for concomitant medications that are substrates of CYP2C19, CYP2C9, and/or CYP3A and have a narrow therapeutic range (Appendix D). Selection of an alternative concomitant medication is recommended.

Caution should also be exercised for concomitant use of certain statin drugs (e.g., rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9.

8.5 Bisphosphonates

Bisphosphonates are permitted.

8.6 Anticoagulants

Caution should be exercised in patients receiving oral rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro. Patients taking warfarin should have international normalized ratio (INR) monitored regularly according to standard institutional practices.

8.7 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. 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.

In vitro data showed that rucaparib is an inhibitor of P-gp and thus patients taking digoxin, a P-gp substrate, should have their digoxin levels monitored regularly via standard clinical practice.

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 9 summarizes the procedures and assessments to be performed for all Part 1 patients except those enrolled into a food-effect PK evaluation cohort.

Table 10 summarizes the procedures and assessments to be performed for all Part 1 patients enrolled into a food-effect PK evaluation cohort.

Table 11 summarizes the procedures and assessments to be performed for all patients enrolled in Part 2.

Table 12 summarizes the timing of ECGs, PK samples (including additional samples for metabolite profiling), PD samples, and dosing of oral rucaparib related to these assessments.

Table 13 summarizes the procedures and assessments to be performed for all patients enrolled in Part 3.

Table 14 summarizes the schedule of dosing and PK sampling for patients in Part 3.

All procedures and assessments are to be completed within ±1 day of the scheduled time point and are synchronized with administration day of oral rucaparib treatment unless indicated.

Table 9. Schedule of Assessments - Part 1: All Cohorts Except Food-Effect Evaluation

Procedure[a]	Screening	Dose-Escalation Evaluation			Optional Treatment-Extension Period	End of Treatment (After Last Dose)	Follow-up (28 [±3] Days After Last Dose)
		Cycle 1			Cycles 2+		
	Day -30 to Day -1	Day -1	Day 1[b]	Days 8, 15, & 22	Day 1[c]		
Informed Consent	X						
Medical/Oncology History	X						
Physical Examination	X		X	X[d]	X	X	
Height	X						
Weight	X		X	X	X	X	
ECOG Performance Status	X		X		X	X	
Vital Signs[e]	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	
12-lead ECG (in Triplicate)[f]	X	X[g]	X[h]	X[h,i]	X	X	
ECHO or MUGA Scan[j]	X						
Hematology[k]	X[l]		X	X	X	X	
Serum Chemistry[m]	X[l]		X	X	X	X	
Serum Pregnancy Test	X[n]					X	
Urinalysis[o]	X						
Tumor Markers (optional)[p]	(X)		(X)		(X)	(X)	
Tumor Scans[q]	X				X[r]	X	
Tumor Samples (optional)[s]	(X)					(X)	
Adverse Events[t]	X	X	X	X	X	X	X
Plasma PK Samples			X[u]	X[u,v]	X[v]		
Duplicate Set of Plasma PK Samples for Metabolite Profiling			(X)[w]	(X)[i,x]			
Oral Rucaparib Dispensation/Administration			X	X	X		

BUN = blood urea nitrogen, CT = computer tomography, EOS = end of study, MRI = magnetic resonance imaging, PET = positron emission tomography, SAE = serious adverse event

[a] = Unless specified, procedure is to be completed within ±1 day of scheduled time point and be synchronized with administration day of rucaparib.

[b] = Any procedures required on Day 1 of Cycle 1, except for the ECGs, may be omitted if completed ≤3 days earlier during the screening period.

[c] = Cycle 2, Day 1 assessments do not need to be repeated if the visit is the same day as Cycle 1, Day 22 or no more than 7 days later. Note: the plasma PK sample should be collected on Day 22 of Cycle 1 only. No additional sample should be collected if a separate Cycle 2, Day 1 visit is required.

[d] = Limited/targeted physical exam to be performed on Days 8 and 15 of Cycle 1.

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

[f] = Predose 12-lead ECGs (in triplicate) will be run for 10 seconds, >2 min apart, with patient resting for 5 min prior to recording.

[g] = At a time point equivalent to the estimated postdose T_{max} of oral rucaparib administered on the following day. This ECG will be time-matched to the 12-lead ECG taken on the following day at estimated T_{max} [2 h after administration] following oral dosing with rucaparib.

[h] = Postdose 12-lead ECG (in triplicate) taken at estimated T_{max} (2 h after administration) and at 7 h after administration of rucaparib on Day 1 and Day 15; 12-lead ECG (in triplicate) on Day 22 (prior to dosing, if Cycle 1, Day 22 = Cycle 2, Day 1).

[i] = Day 15 and Day 22 only.

[j] = To be repeated during treatment period as clinically indicated.

[k] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and must be reviewed by the investigator prior to dosing with rucaparib.

[l] = To be performed ≤14 days prior to the first dose of rucaparib.

[m] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a local laboratory.

[n] = Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤3 days prior to the first dose of rucaparib, .

[o] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal, perform microscopic evaluation to assess abnormal findings.

[p] = Optional: tumor markers appropriate to a patient's cancer diagnosis will be measured by a local laboratory.

[q] = Tumor assessments to consist of clinical examination and appropriate imaging techniques (preferably 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. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

[r] = Tumor scans to be performed within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10. If initial CR or PR noted at Cycle 7 or beyond, confirmatory scans must be performed 4–6 weeks later.

[s] = Tumor tissue samples are optional. Patient must provide consent to provide archival and/or fresh tumor tissue samples at screening and at time of disease progression/treatment discontinuation. For archival tissue, the most recent sample collected prior to treatment should be provided. Refer to the Laboratory Manual for detailed sample collection, preparation, and shipment instructions.

[t] = AEs are recorded from time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs should be followed to resolution.

[u] = PK samples to be collected predose (any time on Day 1; 5-10 min prior to dosing on Day 15) and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) postdose on Days 1 and 15 of Cycle 1.

[v] = PK sample to be collected any time prior to dosing on Days 8 and 22 of Cycle 1, and on Day 1 of Cycles 3-9

[w] = PK sample for metabolite profiling on Day 1 is predose only.

[x] = Duplicate set of PK samples to be collected from first 3 patients enrolled into the RP2D Expansion cohort only. PK samples to be collected predose (5–10 min prior to dosing) and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) postdose.

Table 10. Schedule of Assessments - Part 1: Food-Effect Evaluation Cohort(s) Only

Procedure[a]	Screening	Dose-Escalation Evaluation					Optional Treatment-Extension Period	End of Treatment (After Last Dose)	Follow-up (28 [±3] Days After Last Dose)
		Cycle 1					Cycles 2+		
	Day -30 to Day -1	Day -8[b]	Day -7[b]	Day -1	Day 1	Days 8, 15, & 22	Day 1[c]		
Informed Consent	X								
Medical/Oncology History	X								
Physical Examination	X		X[d]		X	X[d]	X	X	
Height	X								
Weight	X		X		X	X	X	X	
ECOG Performance Status	X		X		X		X	X	
Vital Signs[e]	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	
12-lead ECG (in Triplicate)[f]	X	X[g]	X[h]	X[g]	X[h]	X[h,i]	X	X	
ECHO or MUGA Scan[j]	X								
Hematology[k]	X[l]		X		X	X	X	X	
Serum Chemistry[m]	X[l]		X		X	X	X	X	
Serum Pregnancy Test	X[n]							X	
Urinalysis[o]	X								
Tumor Markers (optional)[p]	(X)				(X)		(X)	(X)	
Tumor Scans[q]	X						X[r]	X	
Tumor Tissue Samples (optional)[s]	(X)							(X)	
Adverse Events[t]	X	X	X	X	X	X	X	X	X
Plasma PK Samples			X[u]		X[u]	X[u,v]	X[v]		
Oral Rucaparib Dispensation/Administration			X		X	X	X		
High-Fat Breakfast					X				

BUN = blood urea nitrogen, CT = computer tomography, EOS = end of study, MRI = magnetic resonance imaging, PET = positron emission tomography, SAE = serious adverse event

[a] = Unless specified, procedure is completed within ±1 day of scheduled time point and be synchronized with administration day of rucaparib.

[b] = Any procedure, except for the ECGs, may be omitted if completed ≤3 days earlier during the screening period.

[c] = Cycle 2, Day 1 assessments do not need to be repeated if visit is same day as Cycle 1, Day 22 or no more than 7 days later. Note: the plasma PK sample should be collected on Day 22 of Cycle 1 only. No additional sample should be collected if a separate Cycle 2, Day 1 visit is required.

[d] = Limited/targeted physical exam to be performed on Day -7 prior to Cycle 1, and on Day 8 and 15 of Cycle 1.

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

[f] = 12-lead ECGs (in triplicate) will be run for 10 seconds, >2 min apart, with patient resting for 5 min prior to recording.

[g] = At a time point equivalent to the estimated postdose T_{max} of oral rucaparib administered on the following day. This ECG will be time-matched to the 12-lead ECG taken on the following day at estimated T_{max} [2 h after administration] following oral dosing with rucaparib.

[h] = Postdose 12-lead ECG (in triplicate) taken at estimated T_{max} (2 h after administration) and at 7 h after administration of rucaparib on Day -7, Day 1 and Day 15; 12-lead ECG (in triplicate) on Day 22 (prior to dosing, if Cycle 1, Day 22 = Cycle 2, Day 1).

[i] = Day 15 and Day 22 only.

[j] = To be repeated during treatment period as clinically indicated.

[k] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and must be reviewed by the investigator prior to dosing with oral rucaparib.

[l] = To be performed ≤14 days prior to the first dose of rucaparib.

[m] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a local laboratory.

[n] = Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤3 days prior to the first dose of rucaparib.

[o] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal, perform microscopic evaluation to assess abnormal findings.

[p] = Optional: tumor markers appropriate to a patient's cancer diagnosis will be measured by a local laboratory.

[q] = Tumor assessments to consist of clinical examination and appropriate imaging techniques (preferably 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. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

[r] = Tumor scans to be performed within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle thereafter, beginning with Cycle 10. If initial CR or PR noted at Cycle 7 or beyond, confirmatory scans must be performed 4-6 weeks later.

[s] = Tumor tissue samples are optional. Patient must provide consent to provide archival and/or fresh tumor tissue sample at screening and at time of disease progression/treatment discontinuation. For archival tissue, the most recent sample collected prior to treatment should be provided. Refer to the Laboratory Manual for detailed sample collection, preparation, and shipment instructions.

[t] = AEs are recorded from time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs should be followed to resolution.

[u] = PK samples to be collected predose (any time on Day -7 and Day 1; 5–10 min prior to dosing on Day 15) and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) postdose on Day -7, Day 1 and Day 15 of Cycle 1.

[v] = PK sample to be collected any time prior to dosing on Days 8 and 22 of Cycle 1, and on Day 1 of Cycles 3-9.

Table 11. Schedule of Assessments - Part 2A and 2B: All Patients

Procedure[a]	Screening	Dosing Period: Cycle 1		Dosing Period: Cycles 2 and Beyond	End of Treatment (After Last Dose)	Follow-up (28 [±3] Days After Last Dose)	Long-term Follow-up
	Day -30 to Day -1	Day 1[b]	Day 15	Day 1			
Informed Consent	X						
Medical/Oncology History	X						
Physical Examination	X	X	X[c]	X	X		
Height	X						
Weight	X	X	X	X	X		
ECOG Performance Status	X	X		X	X		
Vital Signs[d]	X	X	X	X	X		
Prior/Concomitant Medications	X	X	X	X	X		
12-lead ECG (in Triplicate)[e]	X	X[s]		X[s]	X		
Hematology[f]	X[g]	X	X	X	X		
Serum Chemistry[h]	X[g]	X	X	X	X		
Serum Pregnancy Test[i]	X			X	X		
CA-125 Measurement[j]	X	X		X	X		
Urinalysis[k]	X						
Tumor Scans[l]	X			X[m]	X		X[t]
Archival Tumor Tissue[n]	(X)				X		
Adverse Events[o]	X	X	X	X	X	X	
Plasma PK Samples			X[p]	X[q]			
Serum AAG Samples[r]			X[p]	X[q]			
Oral Rucaparib Dispensation/Administration		X	X	X			
Part 2B Only: Survival, Subsequent Treatments, and Secondary Malignancy Monitoring							X[u]

BUN = blood urea nitrogen, CT = computer tomography, EOS = end of study, MRI = magnetic resonance imaging, PET = positron emission tomography, SAE = serious adverse event

[a] = Unless specified, procedure is completed within ±1 day of scheduled time point and is synchronized with administration day of rucaparib.

[b] = At Day 1 of Cycle 1, any procedure may be omitted if completed ≤3 days earlier during the screening period.

[c] = Limited/targeted physical exam to be performed on Day 15 of Cycle 1.

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

[e] = 12-lead ECGs (in triplicate) (predose, where applicable) will be run for 10 seconds, >2 min apart, with patient resting for 5 min prior to recording.

[f] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and must be reviewed by the investigator prior to dosing with rucaparib.

[g] = To be performed ≤14 days prior to the first dose of rucaparib.

[h] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a local laboratory.

[i] = Serum ß-hCG (evaluated by local laboratory) will be performed only on women of childbearing potential at the following time points: ≤ 3 days prior to the first dose of rucaparib, ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond, and at the End-of-Treatment Visit.

[j] = CA-125 as measured by a local laboratory.

[k] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.

[l] = Tumor assessments to consist of clinical examination and appropriate imaging techniques (preferably 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. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Tumor scans will be collected and sent for evaluation by independent radiology review.

[m] = Tumor scans to be performed within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning at Cycle 10. If initial CR or PR is noted prior to start of Cycle 7 or beyond, confirmatory scans must be performed4–6 weeks later.

[n] = A mandatory archival tumor biopsy will be collected from newly enrolled patients and from previously enrolled patients who provide additional consent. Refer to the Pathology Charter for detailed sample handling instructions. May be collected at Any time during study.

[o] = AEs are recorded from time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs should be followed until resolution.

[p] = PK sample to be collected approximately 12 h after the last dose, but prior to the next dose (i.e., typically 5–10 min prior to dosing).

[q] = PK sample to be collected any time prior to dosing for Cycles 2, 3, 5, 7, and 9. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8.

[r] = Serum AAG sample to be collected on the same day as the PK sample.

[s] = Part 2A only

[t] = Part 2B only. For any patient who discontinued from study treatment for reason other than disease progression or death. To be performed within 7 days prior to the start of every 9 weeks of until radiologically confirmed disease progression, death, or initiation of subsequent treatment. Patients who have been on study at least 18 months may decrease the frequency of tumor scans to every 16 (±14 days) weeks.

[u] = All Part 2B patients discontinued from treatment, regardless of reason, should be followed for survival, subsequent therapies, and secondary malignancy every 12 weeks (±7 days) 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. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports).

Table 12. Schedule of Dosing, Electrocardiograms, and Pharmacokinetic Sampling, for Part 1 and Part 2 Patients

Procedure and Time Points	Part 1 Food-Effect PK Cohort(s) Only	Part 1 All Cohorts (Unless Otherwise Specified)							Part 2 All Patients		
	Cycle 1							Cycles 2+	Cycle 1		Cycles 2+
	Day -8	Day -7	Day -1	Day 1	Day 8	Day 15	Day 22	Day 1[a]	Day 1	Day 15	Day 1
Oral Rucaparib Administration[b]		X[c]		X[d]	X	X		X	X	X	X
Plasma PK Samples **(Any Time Prior to Dosing, if Applicable)**		X		X	X		X	X[e]			X
Plasma PK Sample, Predose						X				X	
Plasma PK Samples, Postdose **(15 [±2] min, 30 [±3] min, 1 h [±5 min], 1.5 h [±5 min], 2.5 h [±5 min], 4 h [±15 min], 6 h [±15 min], 8 h [±15 min], 10 h [±30 min], and 24 h [±30 min])**		X		X		X					
Duplicate Set of Plasma PK Samples for Metabolite Profiling, Predose **(Any Time Prior to Dosing)**				(X)[f]							
Duplicate Set of Plasma PK Samples for Metabolite Profiling, Postdose **(15 [±2] min, 30 [±3] min, 1 h [±5 min], 1.5 h [±5 min], 2.5 h [±5 min], 4 h [±15 min], 6 h [±15 min], 8 h [±15 min], 10 h [±30 min], and 24 h [±30 min])**						(X)[f]					
12-Lead ECGs (in Triplicate, >2 min Apart) **(Any Time Prior to Dosing)**							X	X	X		X[g]
12-Lead ECGs (in Triplicate, >2 min Apart) **(At Time Point Equivalent to Estimated Postdose T_{max} [approx. 2 h postdose] of Dose Administered the Following Day)**	X		X								
12-Lead ECGs (in Triplicate, >2 min Apart) **(At Estimated T_{max} [2 h Postdose] and 7 h postdose)**		X		X		X					

[a] = Cycle 2, Day 1 assessments do not need to be repeated if the visit is the same day as Cycle 1, Day 22 or no more than 7 days later. Note: the plasma PK sample should be collected on Day 22 of Cycle 1 only. No additional sample should be collected if a separate Cycle 2, Day 1 visit is required.
[b] = Unless otherwise specified or instructed based on results of food effect PK evaluation, patients may take rucaparib on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal).
[c] = Patients enrolled into a food effect PK evaluation cohort must fast for 10 h prior to, and 2 h after, rucaparib administration.
[d] = Patients enrolled into a food effect PK evaluation cohort must fast for 10 h prior, and 4 h after, rucaparib administration.
[e] = Cycle 2, Day 1 PK sample is the same as the Cycle 1, Day 22 sample.
[f] = Duplicate set of PK samples, pre- and postdose, for metabolite profiling to be collected from first 3 patients enrolled into the RP2D Expansion cohort.
[g] = Part 2A only

Table 13. Schedule of Assessments - Part 3: All Patients

Procedure[a]	Screening	Dosing Period (21 day cycles)				End of Treatment (After Last Dose)	Follow-up (28 [±3] Days After Last Dose)
		Cycle 1			Cycles 2 and Beyond		
	Day -37 to Day -7	Day -7[b]	Day 1[b]	Day 15	Day 1		
Informed Consent	X						
Medical/Oncology History	X						
Physical Examination	X	X	X	X[c]	X	X	
Height	X						
Weight	X	X	X	X	X	X	
ECOG Performance Status	X	X	X		X	X	
Vital Signs[d]	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	
12-lead ECG (in Triplicate)[e]	X					X	
Hematology[f]	X[g]	X	X	X	X	X	
Serum Chemistry[h]	X[g]	X	X	X	X	X	
Serum Pregnancy Test[i]	X				X	X	
Tumor Marker Measurement[j]	X	X	X		X	X	
Urinalysis[k]	X	X	X		X	X	
Tumor Scans[l]	X				X[m]	X	
Archival Tumor Tissue[n]	X					X	
Adverse Events[o]	X	X	X	X	X	X	X
Plasma PK Samples		X	X	X[p]	X[q]		
Randomization to fed/fasted sequence[r]	X						
Serum AAG Samples[s]		X	X	X[p]	X[q]		
Oral Rucaparib Dispensation/Administration		X	X	X[t]	X		
High-Fat Breakfast[u]		(X)	(X)				

BUN = blood urea nitrogen, CT = computer tomography, EOS = end of study, HDL = high density lipoprotein; LDL = low density lipoprotein; MRI = magnetic resonance imaging, PET = positron emission tomography, SAE = serious adverse event

[a] = Unless specified, procedure is completed within ±1 day of scheduled time point and is synchronized with administration day of rucaparib.

[b] = At Day -7 and Day 1 of Cycle 1, any procedure may be omitted if completed ≤3 days earlier during the screening period.

[c] = Limited/targeted physical exam to be performed on Day 15 of Cycle 1.

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

[e] = 12-lead ECGs (in triplicate) (predose, where applicable) will be run for 10 seconds, >2 min apart, with patient resting for 5 min prior to recording.

[f] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and must be reviewed by the investigator prior to dosing with rucaparib.

[g] = To be performed ≤14 days prior to the first dose of rucaparib.

[h] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, lipid panel (total cholesterol, LDL, HDL, and triglycerides), glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a local laboratory.

[i] = Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential at the following time points: ≤ 3 days prior to the first dose of rucaparib, ≤ 3 days prior to Day 1 of every cycle from Cycle 2 and beyond, and at the End-of-Treatment Visit.

[j] = Markers as measured by local and central laboratories at screening and by central laboratory for all other time points.

[k] = Includes dipstick for protein, glucose, blood, pH, and ketones. Microscopic evaluation will be performed routinely.

[l] = Tumor assessments to consist of clinical examination and appropriate imaging techniques (preferably 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. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Tumors scans will be collected and sent for evaluation by independent radiology review.

[m] = Tumor scans to be performed within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning at Cycle 10. If initial CR or PR is noted prior to start of Cycle 7 or beyond, confirmatory scans must be performed 4–6 weeks later.

[n] = Archival tumor tissue will be confirmed available at screening (submitted during study). An optional biopsy sample may be taken at time of disease progression/discontinuation of treatment. Refer to the Pathology Charter for detailed sample handling instructions.

[o] = AEs are recorded from time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs should be followed until resolution.

[p] = First PK/AAG sample to be collected approximately 12 h after the last dose, but prior to the next dose (i.e., typically 5–10 min prior to dosing [see detailed table for additional details]).

[q] = PK sample to be collected any time prior to dosing for Cycles 2, 3, 5, 7, and 9. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8.

[r] = Prior to Day -7 to allow advanced preparation of high fat breakfast for fed condition.

[s] = Serum AAG sample to be collected on the same day as the PK sample.

[t] = Second dose of rucaparib to be given at 12 hours ± 30 minutes after the first (morning dose).

[u] = High fat breakfast will be on either Day -7 or Day 1.

Table 14. Schedule of Dosing and Pharmacokinetic Sampling for Part 3 Patients

Procedure and Time Points	Cycle 1				Cycles 2+
	Day -7	Day 1	Day 15	Day 22	Day 1[a]
Oral Rucaparib Administration[b]	X[c]	X[d]	X		X
Plasma PK Samples **(Any Time Prior to Dosing, if Applicable)**	X	X		X	X[e]
Plasma PK Sample, Predose **(5–10 min Prior to Dosing)**			X		
Plasma PK Samples, Postdose **(15 [±2] min, 30 [±3] min, 1 h [±5 min], 1.5 h [±5 min], 2.5 h [±5 min], 4 h [±15 min], 6 h [±15 min], 8 h [±15 min], 10 h [±30 min], and 24 h [±30 min])**	X	X	X		

[a] = Cycle 2, Day 1 assessments do not need to be repeated if the visit is the same day as Cycle 1, Day 22 or no more than 7 days later. Note: the plasma PK sample should be collected on Day 22 of Cycle 1 only. No additional sample should be collected if a separate Cycle 2, Day 1 visit is required.
[b] = Unless otherwise specified or instructed based on results of food effect PK evaluation, patients may take rucaparib on an empty stomach or with food.
[c] = Patients must fast for 10 h prior to, and 4 h after, rucaparib administration.
[d] = Patients must fast for 10 h prior, and 4 h after, rucaparib administration.
[e] = Cycle 2, Day 1 PK sample is the same as the Cycle 1, Day 22 sample.

9.2 Screening Period (Parts 1-3)

Following written informed consent, and unless otherwise specified, the following assessments will be performed during the 30 day period prior to the first dose of oral rucaparib. Assessments performed prior to patient signing informed consent are acceptable only if confirmed to have been standard of care.

- Medical history, including demographic information (birth date, race, gender, etc.) and smoking status, and oncology history, including date of cancer diagnosis, and any surgical procedures
- Physical examination by body system, height, and weight
- ECOG performance status (Appendix B)
- Vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications
- 12-lead ECG (in triplicate >2 min apart)
- ECHO or MUGA scan (Part 1 Only)
- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], and platelet count) ≤14 days prior to the first day of dosing
- Serum chemistry (total protein, albumin, creatinine, blood urea nitrogen [BUN] or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus) and lipid panel (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides: part 3 only) ≤14 days prior to the first day of dosing
- Tumor marker(s) (optional for all patients in Part 1); CA-125 measurement required for all patients in Part 2; appropriate tumor markers to be collected for all patients in Part 3. ***(Note: tumor marker data will be collected retroactively for all Part 1 patients who were enrolled under other protocol versions)***
- Serum pregnancy test (by local laboratory) ≤ 3 days prior to the first day of dosing for women of childbearing potential
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones). If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings (Parts 1 & 2). In Part 3, urinalysis to be performed ≤14 days prior to the first day of dosing; microscopic evaluation will performed routinely

- Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably computed tomography [CT] scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study.
- AE monitoring (after signing informed consent)

- Tumor tissue sample – archival tissue and/or fresh biopsy are required as follows:
  - Part 1, an optional archival and/or fresh biopsy may be collected
  - Part 2, an archival tumor tissue sample will be required from all newly enrolled patients and will also be collected from previously enrolled patients who provide appropriate consent. The sample is not required to be provided before enrollment, but should be submitted as soon as possible after a patient begins treatment. An optional fresh biopsy may be collected at screening and/or at time of disease progression/treatment discontinuation
  - Part 3, archival tissue will be collected after being confirmed as being available. The sample is not required to be provided before enrollment, but should be submitted as soon as possible after a patient begins treatment. For archival tissue, the most recent sample collected prior to treatment should be provided. Refer to the Laboratory Manual for detailed sample collection, preparation, and shipment instructions. An optional fresh biopsy may be collected at time of disease progression/treatment discontinuation

9.3 Part 1 - Dose-Escalation Evaluation Period

Before enrolling a patient into Part 1, all eligibility criteria must be satisfied. Patients who qualify for the study will be enrolled into the first available cohort.

Unless otherwise specified, all patients in Part 1 will undergo the following procedures and assessments.

9.3.1 Day -8 Prior to Cycle 1 (Food Effect PK Cohort Only)

- Vital signs
- Concomitant medications since screening
- 12-lead ECG (in triplicate >2 min apart) at a time point equivalent to the estimated postdose T_{max} of oral rucaparib (this ECG will be time-matched to the 12-lead ECG taken on Day -7 at estimated T_{max} [2 h postadministration] following dosing with oral rucaparib)
- AE monitoring

9.3.2 Day -7 Prior to Cycle 1 (Food Effect PK Cohort Only)

Patients will be instructed to arrive for their visit having fasted for at least 10 h. The following procedures will be completed before receiving the first dose of oral rucaparib. Any procedure, except for the ECGs, may be omitted if completed ≤3 days earlier during the screening period.

- Physical examination
- Weight
- ECOG performance status
- Vital signs

- Concomitant medications
- Hematology and serum chemistry
- AE monitoring
- PK blood sample (any time prior to dosing)

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients must fast for at least 2 h after dosing. The following procedures will be performed over a 24-h period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min)
- Postdose 12-lead ECG (in triplicate >2 min apart) taken at estimated T_{max} (2 h postadministration) and at 7 h postadministration of oral rucaparib
- AEs experienced by the patient since dosing and/or before leaving the clinic will be documented
- Concomitant medications administered since dosing will be recorded

9.3.3 Day -1 Prior to Cycle 1

The following procedures will be completed on Day -1:

- Vital signs
- Concomitant medications
- 12-lead ECG (in triplicate >2 min apart) at a time point equivalent to the estimated postdose T_{max} of oral rucaparib (this ECG will be time-matched to the 12-lead ECG taken on Day 1 at estimated T_{max} [2 h postadministration] following oral dosing with oral rucaparib)
- AE monitoring

9.3.4 Day 1 of Cycle 1

Patients enrolled into a food effect PK evaluation cohort will be instructed to arrive for their visit having fasted for at least 10 h. All other patients can take rucaparib on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). The following procedures will be completed before oral rucaparib is administered:

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

- Vital signs
- Concomitant medications
- Hematology and serum chemistry
- Tumor marker(s) (optional). ***Note: tumor marker data will be collected retroactively for all Part 1 patients who were enrolled under other protocol versions.***
- AE monitoring
- High-fat breakfast started (and completed within) 30 min prior to dosing with oral rucaparib ***(patients enrolled in a food-effect PK evaluation cohort only)***
- PK blood sample (any time prior to dosing) ***(Note: A duplicate set of samples is to be collected from the first three patients enrolled into the RP2D Expansion cohort. The second sample will serve as the baseline sample for metabolite profiling.)***

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients enrolled into a food effect PK evaluation cohort must fast for at least 4 h after dosing. The following procedures will be performed over a 24 h period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min)
- Postdose 12-lead ECG (in triplicate >2 min apart) taken at estimated T_{max} (2 h after administration) and at 7 h after administration of oral rucaparib
- AEs experienced by the patient since dosing will be documented
- Concomitant medications administered since dosing will be recorded

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal) at about the same time every day. Oral rucaparib should be taken with 8 oz of room temperature water. Patients will record dosing information in their daily dosing diary.

9.3.5 Days 8, 15, and 22 of Cycle 1

Patients will be instructed to refrain from taking their first dose of oral rucaparib at home on the day of their clinic visits because the dose will be taken during the clinic visit.

The following procedures will be completed prior to administration of oral rucaparib on Days 8, 15, and 22 of Cycle 1:

- Physical examination (limited/targeted on Day 8 and Day 15)
- Weight
- Vital signs

- Concomitant medications
- Hematology and serum chemistry
- AE monitoring
- PK blood sample (any time prior to dosing) (Day 8 and Day 22)
- PK blood sample (5–10 min prior to dosing) (Day 15 only)

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal).

On Day 15, the following procedures will be performed over a 24 h period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) ***(Note: A duplicate set of samples is to be collected from the first three patients enrolled into the RP2D Expansion cohort. The second set of samples will be for metabolite profiling.)***
- Postdose 12-lead ECG (in triplicate >2 min apart) taken at estimated T_{max} (2 h after administration) and at 7 h after administration of oral rucaparib
- AEs experienced by the patient since dosing will be documented
- Concomitant medications administered since dosing will be recorded

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal), unless instructed otherwise based on results from PK food-effect analyses, and record dosing information in the daily dosing diary.

9.4 Part 1 - Optional Treatment-Extension Period

Patients may participate in an optional Treatment-extension Period that begins on Day 1 of Cycle 2.

9.4.1 Day 1 of Cycle 2 and Beyond

Note: Cycle 2, Day 1 assessments do not need to be repeated if visit is the same day as Cycle 1, Day 22 or no more than 7 days later.

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

On Day 1 of each cycle, patients participating in the optional Treatment-Extension Period will undergo the following procedures prior to rucaparib administration:

- Physical examination
- Weight
- Vital signs and ECOG performance status
- 12-lead ECG (in triplicate >2 min apart)
- Hematology and serum chemistry
- Tumor marker(s) (optional). ***(Note: tumor marker data will be collected retroactively for all Part 1 patients who were enrolled under other protocol versions).***
- Predose PK blood sample ***(Note: Applies to Cycle 3, Day 1-Cycle 9, Day 1only; the Cycle 2, Day 1 PK sample will be collected as a Cycle 1, Day 22 assessment.)***
- Concomitant medications
- AE monitoring
- Tumor scans (using the same methodology as was used at screening) within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal).

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food, unless instructed otherwise based on results from PK food-effect analyses, and record dosing information in the daily dosing diary.

9.5 Part 2 (Phase II Portion in OC Patients)

Patients will be enrolled into Part 2 once the RP2D has been determined in Part 1 and all patients enrolled into the RP2D Expansion cohort have completed two cycles of treatment or discontinued from the study prior to completing two cycles of treatment.

Before enrolling a patient into Part 2, all eligibility criteria must be satisfied.

9.5.1 Day 1 of Cycle 1

The following procedures will be completed before oral rucaparib is administered. Any procedures that were conducted ≤3 days earlier during the screening period may be omitted.

- Physical examination
- Weight

- ECOG performance status
- Vital signs
- Concomitant medications
- 12-lead ECG (in triplicate >2 min apart) (Part 2A only)
- Hematology and serum chemistry
- CA-125 measurement
- AE monitoring

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water.

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food at about the same time every day, and record dosing information in the daily dosing diary.

9.5.2 Day 15 of Cycle 1

Patients will be instructed refrain from taking their first dose of oral rucaparib at home on the day of their clinic visit until safety assessments have been completed. Patients can then take rucaparib at home or in the clinic on this day.

The following procedures will be completed before oral rucaparib is administered.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Hematology and serum chemistry
- Alpha-1 acid glycoprotein (AAG) serum sample
- PK blood sample (approximately 12 hrs after the last dose, but prior to the next dose [i.e., typically 5–10 min prior to dosing])
- AE monitoring

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food.

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food and record dosing information in the daily dosing diary.

9.5.3 Day 1 of Cycle 2 and Beyond

The following procedures will be completed:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- Concomitant medications
- 12-lead ECG (in triplicate >2 min apart) (Part 2A only)
- Hematology and serum chemistry
- Serum pregnancy test for women of childbearing potential (≤ 3 days prior to start of cycle)
- CA-125 measurement
- AAG serum sample (Any time PK sample is collected)
- PK blood sample (any time prior to dosing) for Cycles 2, 3, 5, 7, and 9. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8
- AE monitoring
- Tumor scans (using the same methodology as was used at screening) within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food.

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food and record dosing information in the daily dosing diary.

9.6 Part 3 (Phase II PK in Patients with Any Advanced Solid Tumor)

Patients enrolled into Part 3 will be treated at the RP2D.

Before enrolling a patient into Part 3, all eligibility criteria must be satisfied.

Screening assessments to be completed prior to day -7 and first dose given. A randomization assignment call must be made before Day -7 in order to allow preparation of a high-fat breakfast in advance of the appropriate day. Patients will be randomized to a sequence of fed on Day -7 and then fasted on Day 1, or, fasted on Day -7 and then fed on Day 1.

All patients enrolled into Part 3 will have plasma samples drawn in order to evaluate the PK profile of 600 mg single dose rucaparib administered as 300 mg tablets in the fed versus fasted state and 600 mg BID (Day 15 of Cycle 1). Patients receive do not receive rucaparib between dose given on morning of Day -7 and dose given on morning of Day 1.

9.6.1 Day -7 Prior to Cycle 1 (single dose fed or fasted PK)

Patients will be instructed to arrive for their visit having fasted for at least 10 h. A PK blood and serum AAG sample must be collected from the patient before they receive the first dose of oral rucaparib, unless a sample was obtained ≤3 days earlier during the screening period. The following procedures will be completed before oral rucaparib is administered.

- Physical examination
  - Weight
  - ECOG performance status
  - Vital signs
- Concomitant medications
- Hematology and serum chemistry
- Urinalysis
- AE monitoring
- Serum AAG sample
- High-fat breakfast if randomized to fed sequence; started (and completed within) 30 min prior to dosing with oral rucaparib

Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients must fast for at least 4 h after dosing. The following procedures will be performed over a 24-h period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min)

9.6.2 Day 1 of Cycle 1 (single dose fasted or fed PK)

Patients will be instructed to arrive for their visit having fasted for at least 10 h. The following procedures will be completed before oral rucaparib is administered.

- Physical examination
- Weight
- ECOG performance status

- Vital signs
- Concomitant medications
- Hematology and serum chemistry (to be collected prior to high-fat breakfast)
- Urinalysis (to be collected prior to high-fat breakfast)
- Tumor markers (as appropriate for tumor type)
- AE monitoring
- PK blood sample (any time prior to dosing)
- Serum AAG sample
- High-fat breakfast started if randomized to fed sequence; started (and completed within) 30 min prior to dosing with oral rucaparib

Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients must fast for at least 4 h after dosing. The following procedures will be performed over a 24 h period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity. Rucaparib tablets will be dispensed to the patient after 24 h blood draw for 600 mg BID dosing.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min)
- AEs experienced by the patient since dosing will be documented
- Concomitant medications administered since dosing will be recorded

Starting on Day 2 Cycle 1 (after 24h sampling point), patients will start dosing with oral rucaparib BID at home (first dose may be at hospital site) on an empty stomach or with food at about the same time every day, and record dosing information in the daily dosing diary.

9.6.3 Day 15 of Cycle 1

Patients will be instructed refrain from taking their first dose of oral rucaparib at home on the day of their clinic visit because the dose will be taken during the clinic visit.

The following procedures will be completed before oral rucaparib is administered.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Hematology and serum chemistry (including lipid panel)

- AAG serum sample
- PK blood sample (5–10 min prior to dosing)
- AE monitoring

Oral rucaparib will be administered with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food

The following procedures will be performed over a 24 h period after morning dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min)
- AEs experienced by the patient since dosing will be documented
- Concomitant medications administered since dosing will be recorded

Patients will continue dosing with oral rucaparib BID at home on an empty stomach or with food and record dosing information in the daily dosing diary. The second dose of Day 15 will be taken 12(±30 min) hours after the morning dose.

9.6.4 Day 1 of Cycle 2 and Beyond

The following procedures will be completed:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- Concomitant medications
- Hematology and serum chemistry (including lipid panel)
- Serum pregnancy test for women of childbearing potential (≤ 3 days prior to start of cycle)
- Urinalysis
- Tumor markers (as appropriate for tumor type)
- AAG serum sample (any time PK sample is collected)
- PK blood sample (any time prior to dosing) for Cycles 2, 3, 5, 7, and 9. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8
- AE monitoring

- Tumor scans (using the same methodology as was used at screening) within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10. Additional consent will be taken for tumor scans to be collected and stored for possible evaluation by independent radiology review

Rucaparib tablets will be dispensed to the patient. Oral rucaparib will be administered BID with 8 oz (240 mL) of room temperature water. Patients can take rucaparib on an empty stomach or with food.

Patients will continue dosing with oral rucaparib at home on an empty stomach or with food and record dosing information in the daily dosing diary.

9.7 End-of-Treatment Visit (Parts 1-3)

The following procedures will be performed for all patients after the last dose of oral rucaparib:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- Concomitant medications since last visit
- ECGs (in triplicate >2 min apart)
- Hematology and serum chemistry (including lipid panel)
- Serum pregnancy test for women of childbearing potential
- Urinalysis (Part 3 only)
- Tumor marker(s) (optional for all patients in Part 1; in Part 2 CA-125 required for all patients and in Part 3, appropriate markers according to tumor type e.g., CA-125 or CEA are collected). ***(Note: tumor marker data will be collected retroactively for all Part 1 patients who were enrolled under other protocol versions).***
- Serum pregnancy test for women of childbearing potential
- Tumor scans (using the same methodology as was used at screening). Tumor scans to be collected and stored for possible evaluation by independent radiology review (***for Part 2A, Part 2B, and Part 3 patients***)
- Tumor tissue sample – archival and/or fresh biopsy. Refer to the Laboratory Manual for detailed sample collection, preparation, and shipment instructions.
  - Part 1, an optional fresh biopsy may be collected at time of disease progression/treatment discontinuation
  - Part 2, an archival tumor tissue sample will be required from all newly enrolled patients and will also be collected from previously enrolled patients who provide appropriate

consent. The sample is not required to be provided before enrollment, but should be submitted as soon as possible after a patient begins treatment. An optional fresh biopsy may be collected at time of disease progression/treatment discontinuation

- Part 3, an optional fresh biopsy may be collected at time of disease progression/treatment discontinuation

- AE monitoring

9.8 Follow-up Visit

The following procedures will be performed at 28 (±3) days after the last dose of rucaparib:

- AE monitoring (ongoing SAEs and AEs of special interest [AESI]should be followed until resolution, stabilization, or patient is lost to follow-up)

9.9 Long-term Follow-up

For Part 2B patients only:

- All Part 2B patients discontinued from treatment, regardless of reason, should be followed for survival, subsequent anti-cancer treatments, and secondary malignancy monitoring every 12 weeks [±7 days] 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. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports).
- Tumor scans (using the same methodology as was used at screening) for any patient who discontinued from study treatment for reason other than disease progression or death to be performed within 7 days prior to the start of every 9 weeks until radiologically confirmed disease progression, death, or initiation of subsequent treatment. Patients who have been on study at least 18 months may decrease the frequency of tumor scans to every 16 weeks [±14 days]

9.10 Methods of Data Collection

9.10.1 Pharmacokinetic Evaluations

9.10.1.1 Pharmacokinetic Blood Sample Collection in Part 1

For patients in Part 1, 4 mL venous blood samples for the PK analysis of oral rucaparib will be drawn at the following time points:

- Day -7 prior to Cycle 1 ***(food-effect PK evaluation cohort[s] only***): Prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) after dosing

- Day 1 of Cycle 1 ***(all patients in Part 1)***: Prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) after dosing
  - An additional 4 mL sample will be collected prior to rucaparib administration from the first 3 patients enrolled into the RP2D Expansion cohort. This will serve as the baseline sample for subsequent profiling of circulating metabolites of rucaparib that will be performed on PK samples collected on Day 15 of Cycle 1.
- Day 8 of Cycle 1 ***(all patients in Part 1)***: Prior to rucaparib administration
- Day 15 of Cycle 1 ***(all patients in Part 1):*** At 5–10 min prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) after dosing
  - In order to profile circulating metabolites of rucaparib at steady state, additional 4 mL samples will be collected pre- and postdose (at the same time points as noted above) from the first three patients enrolled into the RP2D Expansion cohort.
- Day 22 of Cycle 1 ***(all patients in Part 1)***: Prior to rucaparib administration ***(Note: This sample is equivalent to Day 1 of Cycle 2.)***
- Day 1 of Cycle 3-Cycle 9 (all patients in Part 1 who opt to continue with rucaparib treatment for additional cycles), prior to rucaparib administration

9.10.1.2 Pharmacokinetic Blood Sample Collection in Part 2

For patients in Part 2, 4 mL venous blood samples for the PK analysis of rucaparib will be drawn at the following time points:

- Day 1 of Cycles 2, 3, 5, 7, and 9, prior to dosing with rucaparib. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8
- Day 15 of Cycle 1, 5–10 min prior to dosing with rucaparib

9.10.1.3 Pharmacokinetic Blood Sample Collection in Part 3

For patients in Part 3, 3 mL venous blood samples for the PK analysis of oral rucaparib will be drawn at the following time points:

- Day -7 prior to Cycle 1: Prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) after dosing
- Day 1 of Cycle 1: Prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 10 h (±30 min), and 24 h (±30 min) after dosing
- Day 15 of Cycle 1***:*** At 5–10 min prior to rucaparib administration, and at 15 (±2) min, 30 (±3) min, 1 h (±5 min), 1.5 h (±5 min), 2.5 h (±5 min), 4 h (±15 min), 6 h (±15 min), 8 h

(±15 min), 10 h (±30 min), and 24 h (±30 min) after morning dosing (second dose of rucaparib is given 12 h ±30 min after first [morning] dose)

- Day 22 of Cycle 1: Prior to rucaparib administration ***(Note: This sample is equivalent to Day 1 of Cycle 2.)***

- Day 1 of Cycles 2, 3, 5, 7, and 9, prior to dosing with rucaparib. If dosing is held for toxicity or any other reason, PK sample should still be collected at the end of treatment Cycles 1, 2, 4, 6, and 8

9.10.1.4 Pharmacokinetic Evaluations

PK evaluation will be based on the determination of (not limited to) AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and elimination rate constant (k_{el}), volume of distribution at steady state after non-intravenous administration (V_{ss}/F), and total plasma clearance after oral administration (Cl/F).

Central laboratories will be used for bioanalysis of oral rucaparib and its metabolites in human plasma. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

9.10.2 AAG Measurement

For all patients in Parts 2 & 3of the study, serum samples for AAG analysis will be collected pre-dose on the same days as PK blood samples.

9.10.3 Tumor Tissue Samples

FFPE fresh and/or archival tumor tissue samples at screening and fresh biopsy at time of disease progression/treatment discontinuation will be optional for all patients in Part 1 of the study. Additional consent will be required.

For patients in Part 2, an archival biopsy will be collected from all newly enrolled patients and from previously enrolled patients who provide appropriate consent. The archival biopsy can be collected at any time during the study. A biopsy sample at screening and/or time of disease progression/discontinuation of treatment is optional.

For patients in Part 3, an archival biopsy will be confirmed as available at screening (mandatory for study entry) and subsequently submitted during the study as soon as possible after treatment begins. An optional biopsy sample may be taken at time of disease progression/discontinuation of treatment.

For fresh tissue, core needle biopsies should be collected from either primary tumor or an accessible lesion. If a fresh tissue sample is not collected, an archival tumor tissue sample (most recent sample collected prior to treatment) should be provided. Scrolls (for RNA extraction) and slides (for immunohistochemistry) will be prepared locally. Information for tumor tissue collection and preparation will be provided in a laboratory manual.

Analysis of the tumor tissue samples may include but not be limited to:

- DNA extraction and sequencing in order to identify if a patient has a *BRCA* reversion or other mutation(s) that may be associated with response or resistance to rucaparib
- Gene expression profiling on extracted RNA to potentially identify a signature associated with response to rucaparib
- Immunohistochemistry analysis of tissue to determine if an immunohistochemistry assay can be developed to accurately identify homologous recombination repair deficiency in *gBRCA* patients

9.10.4 Safety Evaluations

9.10.4.1 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. Patients will be monitored for AEs during study participation (beginning at the time informed consent is obtained) and until 28 days after the last dose of oral rucaparib. Any ongoing SAEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE[2] grading system and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

9.10.4.2 Clinical Laboratory Investigations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. The panels of laboratory tests to be performed are shown below:

Hematology: Hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count per the three schedules of evaluation at screening, during treatment, and at the end-of-study visit. Hematology results must be reviewed by the investigator prior to the start of treatment with oral rucaparib.

Clinical Chemistry: Total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, lipid panel (total cholesterol, LDL, HDL, and triglycerides), glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus per the three schedule of evaluations at screening, during treatment, and at the end-of-study visit.

Urinalysis: Performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only (Parts 1 & 2). In Part 3, urinalysis is performed also at day 1 of each cycle and at EOT visit; microscopic evaluation shall be performed routinely.

Serum ß-hCG Pregnancy Test: Performed on women of childbearing potential ≤ 3 days before Day 1 Cycle 1, ≤ 3 days prior to Day1 of every cycle from Cycle 2 and beyond, and at the end-

of-treatment visit. A negative result must be confirmed by a physician before the first dose of oral rucaparib can be administered.

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

9.10.4.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. All vital signs will be obtained after the patient has been resting for at least 5 min. Vital signs will be performed at screening and at each study visit including the end-of-study visit.

9.10.4.4 12-Lead Electrocardiograms

For patients enrolled in Part 1, 12-lead ECGs (10 second ECG tracings collected in triplicate [>2 min apart]) will be taken at the following time points:

- Screening (within 30 days prior to first rucaparib dose)
- Day -8 prior to Cycle 1 ***(food-effect PK evaluation cohort[s] only)***: at a time point that will match estimated T_{max} (2 h) following administration of oral rucaparib on Day -7
- Day -7 prior to Cycle 1 ***(food-effect PK evaluation cohort[s] only:*** at the estimated T_{max} (2 h) postdose, and at 7 h postdose
- Day -1 prior to Cycle 1 ***(all Part 1 patients)***: at a time point that will match estimated T_{max} (2 h) following administration of oral rucaparib on Day 1
- Day 1 of Cycle 1 ***(all Part 1 patients)***: at the estimated T_{max} (2 h) postdose, and at 7 h postdose
- Day 15 of Cycle 1 ***(all Part 1 patients)***: at the estimated T_{max} (2 h) postdose, and at 7 h postdose
- Day 22 of Cycle 1 ***(all Part 1 patients):*** prior to dosing, if same date as Day 1 of Cycle 2.
- Day 1 of Cycles 2 and beyond ***(all Part 1 patients):*** prior to dosing
- End-of treatment

In addition, patients in Part 1 receiving antiemetic medications known to produce QT prolongation will require additional ECG measurements at estimated T_{max}. ECGs should be performed approximately 2, 4, and 6-7 hours after dosing with rucaparib when the patient begins treatment with the antiemetic and again at the same timepoints 1 to 2 weeks later.

ECGs should be performed after the patient has been resting for at least 5 min. The 12-lead ECGs will be analyzed at a central ECG laboratory. Details on recording ECGs and preparation for central interpretation will be included in the investigator's file. The Sponsor will allow local ECG testing once sufficient centrally obtained data has been collected.

For patients enrolled in Part 2, 12-lead ECGs (10 second ECG tracings collected in triplicate [>2 min apart]) will be taken at the following time points:

- Screening (within 30 days prior to first rucaparib dose)
- Day 1 of Cycle 1 and Day 1 of Cycles 2 and beyond: prior to dosing (Part 2A only)
- End-of treatment

For patients enrolled in Part 3, 12-lead ECGs (10 second ECG tracings collected in triplicate [>2 min apart]) will be taken at the following time points:

- Screening (within 30 days prior to first rucaparib dose)
- End-of treatment

9.10.4.5 Body Weight and Height

Height will be measured during the screening visit only. Weight will be measured at most clinic visits (the patient should be in light indoor clothes).

9.10.4.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Physical examinations will be performed at screening (complete) and at most study visits (limited as appropriate).

9.10.4.7 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at screening, on Day 1 of each cycle, and at the end-of-study visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.10.5 Efficacy Evaluations

9.10.5.1 Tumor Assessments

For Part 1 and Part 2, tumor assessments will be performed at screening, within 7 days prior to the start of Cycles 3, 5, and 7, within 7 days prior to the start of every three cycles thereafter, beginning with Cycle 10, and at the end-of-treatment visit.

For Part 2B, tumor assessments will also be performed during the long-term follow-up period for any patient who discontinued from study treatment for reason other than disease progression or death, within 7 days prior to the start of every 9 weeks until radiologically confirmed disease progression, death, or initiation of subsequent treatment. Patients who have been on study at least 18 months may decrease the frequency of tumor scans to every 16 weeks (±14 days).

For Part 3, tumor scans will be performed at screening, within 7 days prior to the start of Cycles 3, 5, and 7, and within 7 days prior to the start of every three cycles thereafter, beginning with Cycle 10.

If initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4–6 weeks later. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).

Tumor 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); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. For patients in Part 2 and Part 3, tumor scans will be collected for possible evaluation by independent radiology review.

9.10.5.2 Tumor Markers

In Part 1, tumor markers are optional.

In Part 2, CA-125 will be collected at screening, on Day 1 of every cycle, and at the end of treatment visit, performed by a certified local laboratory.

In Part 3 tumor markers appropriate to the tumor type will be collected at screening, on Day 1 of every cycle, and at the end of treatment visit. Appropriate markers are those that are routinely collected to monitor progress of disease eg CA-125 in ovarian cancer; Carcinoembryonic Antigen (CEA) in colon cancer.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, 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.

For the purposes of this study, disease progression of the patient's tumor with new or worsening symptoms must be documented as an AE. However, disease progression documented solely by radiographic evidence with no new or worsening symptoms will not require reporting as an AE.

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 nonleading question (e.g., "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF (not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (including after informed consent is given and prior to dosing) that:

- Results in death. Death may occur as a result of the underlying disease process. Nevertheless, any event resulting in death during the reporting period must be treated as an SAE and reported as such. All deaths occurring within 28 days of the last administration of oral rucaparib will be reported as SAEs.
- 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/birth defect.

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or seizures that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

10.3 Definition of an Adverse Event of Special Interest (AESI)

An AE of special interest (serious or nonserious) is one 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 (e.g., health authorities or ethics committees) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib Investigator's Brochure. These AESIs are to be reported to the sponsor expeditiously (see Section 10.9 for reporting instructions).

10.4 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore are not required to be reported to the Sponsor:

- Pre-planned or elective hospitalization, including social and/or convenience situations (e.g., respite care).
- Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency room, but is not admitted to a ward).
- Overdose of study drug or concomitant medication, unless there is an AE that meets SAE criteria (e.g., hospitalization), as a direct consequence of the overdose. This should be entered as Overdose - followed by the appropriate AE/SAE term.
- Events of disease progression of the patient's underlying cancer as well as events clearly related to disease progression (i.e., signs and symptoms) should not be reported as a SAE unless the outcome is fatal and occurs during the safety reporting period. If the event has a fatal outcome during the safety reporting period, then the event of Progression of Disease must be recorded as an AE/SAE with CTC Grade 5 (fatal outcome) indicated.
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as a SAE.

10.5 Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

A clinical laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The abnormality is considered clinically significant by the investigator.

- The abnormality is of a degree that requires active management (change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

10.6 Pregnancy or Drug Exposure During Pregnancy

Patients should be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib. This also applies to male patients whose partners become pregnant in the same timeframe. Women who become pregnant during the study will discontinue rucaparib immediately and the event will be reported on a specific Pregnancy Report Form in the same reporting timeframe as an SAE (Section 10.9). The pregnancy will be followed to term, any premature terminations or obstetric complications reported, and the status of mother and child will be reported to the sponsor as soon as possible after delivery.

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

Any AE that occurs after the first dose of study drug to 28 days after receiving the last dose of oral rucaparib will be recorded on the AE eCRF. In addition, any AE/SAE that occurs after informed consent is obtained and is deemed related to a screening procedure for the study should also be reported. 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. For example, fever, headache, and nasal discharge may be reported as coryza, if that is a reasonable diagnosis.

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).

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

SAEs that occur after informed consent or within 28 days after receiving the last dose of rucaparib, and all AESIs, whether or not related to rucaparib, must be reported to the sponsor's SAE contact within 24 hours of knowledge of the event. After the 28-day window after treatment discontinuation, only SAEs assessed as related to study drug and all AESIs, irrespective of causality, should be reported. This should be done by faxing or emailing the completed SAE/AESI report to the Sponsor/designee contact provided on the SAE/AESI report form. Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.9.

10.7.1 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE Version 4.0 grading scale.[2] For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, or life threatening 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.
- Life threatening events require urgent intervention to prevent potentially fatal consequences

10.7.2 Relationship of Adverse Events to Investigational Medicinal Products

The causal relationship between the study medication and the AE must be characterized as not related, unlikely, possible/probable, or definitely by the investigator. The following definitions will help guide the cause-and-effect assessment.

Not Related	An AE that, after consideration, is clearly due to extraneous causes (diseases, environment, etc.), which should be specified, if known.
Related	An AE that follows a reasonable temporal relationship to administration of rucaparib. It follows a known response pattern to the suspected drug. It cannot be explained by alternative etiologies It is confirmed with a positive rechallenge or supporting laboratory data.

10.7.3 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

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

Outcome

- Recovered
- Recovered with sequelae
- Improved
- Ongoing
- Death

- Lost to follow-up

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

All AEs 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. All SAE/AESI should be followed until resolution or stabilization, or until patient is lost to follow-up.

10.9 Regulatory Aspects of Adverse Event Reporting

SAEs, AESIs, and pregnancy must be reported to the Sponsor's SAE designee within 24 hours of knowledge of the event, according to the procedures below. It is important that the investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The Serious Adverse Event/Adverse Event of Special Interest (SAE/AESI) Report Form must be used for reporting SAEs and AESIs, and the Pregnancy Report Form must be used for reporting pregnancies.

Additional information should be reported via facsimile to the number above. Further details on SAE/pregnancy reporting can be found in the investigator's file.

Clovis Oncology, Inc. (Clovis Oncology), or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to 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 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In accordance with the European Commission Clinical Trials Directive (2001/20/EC), Clovis Oncology 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.

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

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

PK-Evaluable Population (Parts 1 and 3 only)—all patients who have received at least one dose of rucaparib and have had adequate PK assessments drawn for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.

Food-Effect PK Evaluable Population (Parts 1 and 3 only)—all patients enrolled into a food effect PK evaluation cohort of the study who received rucaparib on both Day 7 and Day 1 (Cycle 1) complied with the fed and fasted requirements, and have sufficient PK data for a comparison to be made between the fasted and fed state.

ECG-Evaluable Population (Part 1 only)—all patients who have received at least one dose of rucaparib and have had adequate PK and ECG assessments performed for determination of the ECG effects in relationship to the PK of rucaparib.

Safety Population—all patients who have received at least one dose of rucaparib.

DLT-Evaluable Population (Part 1 only)—all patients enrolled into Part 1 of the study who received at least 17 complete days of rucaparib and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.

Efficacy-Evaluable Population—all patients who met eligibility criteria, received at least one dose of rucaparib, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment.

11.2 Statistical Methods

11.2.1 General Considerations

The summary tables will be presented for all treated patients by each of the Parts of the study and by appropriate dose groups.

Quantitative variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and/or frequency and percentages for medically relevant categories. 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 will be presented along with the Kaplan-Meier estimates of 3, 6, 9, and 12 month PFS rates. The number of patients with events and the number of censored patients will also be presented.

Individual patient data listings will be provided to support summary tables. All data will be used to their maximum possible extent but without any imputations for missing data.

A statistical analysis plan (SAP) will be available prior to the start of Part 2 of the study. Any deviations from the statistical methods given in the study protocol will be described and justified in the SAP.

All statistical analyses will be conducted with the SAS® System.

11.2.2 Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages.

11.2.3 Baseline Characteristics

Baseline characteristics and demographic data will be summarized for the safety population.

11.2.4 Efficacy Analyses

The efficacy endpoints in each of the parts of the study will be evaluated using RECIST Version 1.1.

11.2.4.1 Overall Response Rate - Primary Endpoint (Part 2)

A primary efficacy endpoint in Part 2 of the study (ORR) is the best overall response recorded from the start of the treatment until disease progression or recurrence. The ORR will be summarized for the tumor-evaluable population enrolled in Part 2 with frequencies and percentages.

11.2.4.2 Secondary Analyses and Endpoints in Part 2 and 3

11.2.4.2.1 ORR per RECIST v 1.1 and Gynecologic Cancer Intergroup (GCIG) CA-125 Criteria (Part 2)

The proportion of patients with the best response by RECIST v 1.1[27] of 'Complete Response' or 'Partial Response' or response according to the GCIG CA-125[28, 29] criteria will be summarized with number of patients and percent and for each response category.

11.2.4.2.2 Tumor Marker (CA-125) Response Rate Based on GCIG CA-125 Criteria (Part 2)

Only patients with elevated level as baseline will be used for this analysis. The incidence of patients with a response (i.e., at least 50% reduction from baseline which is confirmed at a second post-baseline value) in tumor marker CA-125 will be summarized. The time to CA-125 may also be summarized with Kaplan-Meier methodology where the time to CA-125 is defined as duration between the date of first study drug to the date of the first CA-125 response value (at least 50% reduction). If the patient does not have a response they are censored at the last date of cancer antigen measurement.

11.2.4.2.3 Progression-free Survival (PFS) (Part 2)

PFS will be calculated as 1+ the number of days from the date of first dose of study drug 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 (i.e., radiologic assessment) or date of first dose of study drug if no tumor assessments have been performed. PFS will be summarized using Kaplan-Meier methodology.

11.2.4.2.4 Duration of Response - Secondary Endpoint (Part 2)

Duration of response for CR and PR, a secondary endpoint in Part 2, will be measured from the date that any of these best responses is first recorded until the first date that PD is objectively documented. Duration of response will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically.

11.2.4.2.5 Overall Survival (Part 2B)

Overall survival is defined as the 1+ the number of days from the date of first dose of study drug to death, due to any cause. Patients without a documented event of death will be censored on the date of their last visit. Overall survival will be summarized using Kaplan-Meier methodology time from randomization until death from any cause, and is measured in the intent-to-treat population.

11.2.4.2.6 Evaluation of Antitumor Activity – Secondary Endpoint (Parts 1 and 3)

No formal statistical analysis of efficacy will be performed in Part 1. For patients with measurable disease, response to treatment according to RECIST Version 1.1 will be reported via descriptive statistics by dose level.

11.2.4.2.6.1 Changes in Tumor Markers Applicable to Patient's Tumor Type (Part 1 and 3)

Changes in tumor markers applicable to a patient's tumor type will be summarized with summary statistics and may be analyzed in accordance to corresponding tumor marker responder criteria.

11.2.4.3 Exploratory Endpoints in Part 2

11.2.4.3.1 Explore the Association Between Genomic Alterations Identified in Tumor Tissue and Clinical Outcome (Part 2)

The association between mutational status of BRCA1/2 and other homologous recombination genes, including genomic scarring/LOH assessment in tumor tissue will be evaluated for the response by RECIST v1.1 and/or CA-125. This will be done by evaluating all the efficacy endpoints by mutational status for Part 2.

11.2.5 Pharmacokinetic Analyses

As a primary endpoint in Part 1 and Part 3 of the study, PK parameters will be determined using noncompartmental methods. AUC from Time 0 to the last observation will be calculated using the trapezoid rule. The k_{el} will be calculated using log-linear regression on the terminal part of the concentration time curve. The terminal half-life and the AUC from the last observation to infinity will be calculated from the estimated k_{el}. Other parameters to be determined are C_{max}, T_{max}, V_{ss}/F, and Cl/F.

As a secondary endpoint, the effect of food on PK parameters including, but not limited to, C_{max} and AUC, will be compared using linear mixed effect model.

11.2.6 Exploratory Analysis - Relationship Between PK and QTc

As an exploratory endpoint of the study, the relationship between the concentration of oral rucaparib (PK) and potential changes in QTc will be studied. A linear and nonlinear mixed effect modeling approach will be used to quantify the relationship between the plasma concentration and the ΔΔQTc (time-matched, on-treatment to pretreatment difference in QTc interval, baseline-adjusted). Plots of the mean QT/QTc versus drug concentrations and a concentration-QT variables correlation will be explored.

11.2.7 Exploratory Analysis - Metabolite Profiling at the Recommended Phase 2 Dose

As an exploratory endpoint of the study, additional plasma samples will be collected on Day 15 from three patients enrolled in the RP2D Expansion cohort. Individual pooled plasma samples, one from each of these patients, will be prepared using the method proposed by Hamilton.[7] The pooled plasma samples will be further processed before being analyzed by high-performance liquid chromatography coupled in-line with ultraviolet spectrophotometric and tandem mass spectrometric detection (HPLC-UV-MS/MS).

11.2.8 Safety Analyses

The safety analyses will be performed using the safety population (all patients who have received at least one dose of rucaparib).

11.2.8.1 Extent of Exposure

The following will be summarized by study part (i.e., Part 1, 2, and 3) and by dose group using descriptive statistics:

- Number of patients receiving at least one dose
- Number of patients at each dose group, average dose amount
- Number of cycles initiated
- Number of dose reductions/delays

- Number of dose interruptions

The number of patients at each dose group will be summarized with frequencies and percentages; the average dose will be summarized with descriptive statistics and frequency counts for relevant categories. The number of cycles initiated will be investigated by summarizing the number of cycles started by each patient in each period. The number of patients with at least one dose reduction/delay or interruption will be summarized with frequencies and percentages.

11.2.8.2 Adverse Events

The safety analyses will be performed using the safety population for each part of the study separately.

AE coding will be performed using the Medical Dictionary for Drug Regulatory Activities. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Treatment-emergent AEs are defined as AEs with an onset date on or after the date of first dose of rucaparib until the date of the last rucaparib dose plus 28 days. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced treatment-emergent AEs for each system organ class and preferred term will be presented by dose group. Multiple instances of the treatment-emergent AEs in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one treatment-emergent AE will also be summarized by dose group.

Separate tables will present the following by dose group:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Dose-limiting toxicity AEs
- Serious treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of oral rucaparib
- Treatment-emergent AEs resulting in interruption or reduction/delay of rucaparib

The incidence of treatment-emergent AEs will be summarized by relationship to oral rucaparib using “treatment-related” and “not treatment-related” categories. The category of treatment-related is defined as a relationship of Possible/Probable, Definite, or Missing. 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 intensity toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing intensity 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 one treatment-emergent AE of the given grade will be summarized.

Non-treatment-emergent AEs (pretreatment and post-treatment) will be presented in the by-patient data listings.

11.2.8.3 Clinical Laboratory Evaluations

The clinical laboratory evaluations will be summarized using the safety population for each part of the study separately.

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in Systeme International units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of oral rucaparib. The on-treatment period will be defined as the day after the first dose of oral 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 descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the treatment period by dose group. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group. 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 (i.e., those that meet Grade 3 or 4 criteria according to CTCAE) by dose group.

11.2.8.4 Vital Sign Measurements

The vital signs measurements will be summarized using the safety population for each part of the study separately.

The baseline vital sign measurement will be defined as the last value prior to or on the day of the first dose of rucaparib. The on-treatment period will be defined as the day after 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, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period by dose group. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group.

11.2.8.5 12-Lead Electrocardiograms

From ECGs conducted in Part 1 of the study, ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QTc intervals from the pretreatment visit and treatment period visits will be classified as ≤450 msec, >450 to ≤480 msec, >480 to ≤500 msec, and >500 msec. For each patient's maximum change from the pretreatment ECG visit for QT and QTc, intervals will be classified into <30 msec, ≥30 to <60 msec, and ≥60 msec. The number and percentage of patients in each classified category will be presented. Additional endpoints will include abnormal T waves and U waves and other ECG intervals and diagnostic parameters.

Descriptive statistics will be used to summarize other ECG parameters of PR, QRS, QT, and RR interval, and the corresponding changes from pretreatment ECG visit at each time point. Plots of the mean QT/QTc over time for Day 1 and Day 15 of Cycle 1/pretreatment ECG day measurements will be provided.

11.2.8.6 Other Safety Measurements

The body weight and ECOG will be summarized using the safety population for each part of the study separately.

Body weight and ECOG performance status will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Concomitant medications/ procedures will be tabulated and summarized.

11.3 Interim Analysis

No formal interim analyses will be performed.

11.4 Sample Size Considerations

The total patient enrollment planned for this study is approximately 140 patients: 56 patients were enrolled in Part 1. Up to 41 evaluable patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian cancer, fallopian tube, or primary peritoneal associated with a *gBRCA* mutation will be enrolled in Part 2A. Up to 40 evaluable patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with evidence of a deleterious *BRCA* mutation (germline or somatic) will be enrolled in Part 2B. Approximately 20 evaluable patients with an advanced solid tumor, inclusive of lymphoma, with evidence of a *BRCA* mutation (germline or somatic) will be enrolled into Part 3.

Clinical trials of olaparib in recurrent ovarian cancer associated with a *gBRCA* mutation demonstrated ORRs of 13-41%.[13, 25, 26] For the part of the study evaluating rucaparib in platinum-sensitive, relapsed, high-grade serous and endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *gBRCA* mutation, an ORR of 20% will be set as the target.

11.4.1 Sample Size Justification for Part 2A

The study will use a Simon 2-stage design to evaluate the efficacy of rucaparib in Part 2 (Phase II portion). Initially, 21 patients will be treated in Stage 1; if two or more patients in Stage 1 have an objective response (CR or PR), then the remaining 20 patients will be treated in Stage 2. If fewer than two patients in Stage 1 have an objective response, then no further patients will be enrolled.

Characteristics of the Simon 2-stage design include:

- 5% probability of accepting a poor drug
- 90% probability of accepting a good drug
- ORR of 5% for a poor drug
- ORR of 20% for a good drug
- A promising drug will have five or more patients with an objective response (CR or PR) out of 41 patients at the end of Stage 2.

The criteria for Stage 1 success were met in April 2014, and Stage 2 is ongoing with total enrollment of 41 evaluable patients completed in April 2015.

11.4.2 Sample Size Justification for Part 2B

The efficacy of rucaparib in ovarian cancer patients with a deleterious *BRCA* mutation (germline or somatic) who received ≥3 prior chemotherapy regimens and were treated with 600 mg BID rucaparib in Studies CO-338-017 (ARIEL2) and Part 2A of CO-338-010 has been evaluated. In this group, which included both patients with platinum-sensitive and platinum-resistant disease, ORRs of 47% (RECIST) and 73% (RECIST & GCIG CA-125) have been observed, suggesting that rucaparib may be a suitable treatment alternative in this patient population with advanced disease and limited treatment options.

The rationale for evaluating an additional *BRCA*-mutant OC cohort in this study is to better characterize the efficacy and safety in a heavily pre-treated patient population with a deleterious *BRCA* mutation (germline or somatic). An ORR ≥20% in this population would be worthy of further exploration. The table below provides 95% confidence intervals (CIs) for ORRs of 30% to 50% assuming a sample size of 40 patients.

Confidence Intervals for Observed Response Rates

ORR(%)	[95% CI]
30	17,47
40	25, 57
50	34,66

CI=Confidence intervals of ORR using Clopper-Pearson methodology.[6]

Therefore with the sample size of 40 patients an observed ORR of 30% would show similar response as current treatment, however, an observed ORR of 40% or greater has a 95% CI which exceeds the 20%.

11.4.3 Sample Size Justification for Part 3

For Part 3, the study will be an initial randomized, two treatment, two period, crossover design, to explore food effect, with subsequent continuous BID dosing; it is estimated that enrolling approximately 20 evaluable patients will provide sufficient data for PK analysis.

12 PATIENT DISPOSITION

12.1 Patient Discontinuations

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

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Progression of patient's underlying disease
- 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
- A positive pregnancy test at any time during the study
- Increase in QT/QTc of >60 msec over baseline or QTc >500 msec

In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of oral rucaparib must be documented in the eCRF and source documents. To the extent possible, follow-up procedures should be performed on all patients who receive rucaparib. The follow-up visit should occur 28 (±3) days following the last dose of rucaparib. Patients will be followed for 28 days after the last dose of rucaparib for safety; those with ongoing SAEs will be followed until either resolution or stabilization has been determined.

12.2 Study Stopping Rules

If ≥33% of patients in the RP2D Expansion cohort experience a DLT, then enrollment into the RP2D Expansion arm will stop and a lower dose will be explored.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki.

13.1.1 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 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.

U.S.-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered at www.clinicaltrials.gov using the Protocol Registration System.

13.1.2 Independent Ethics Committee/Institutional Review Board

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.

Clovis Oncology 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 will be transmitted to Clovis Oncology. 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 informed consent form, 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.

13.2 Confidentiality of Information

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and the IRB. The investigator must keep logs on screened and enrolled patients. In addition, the investigator must have a list where the identity of all treated patients can be found.

The investigator agrees that all information received from Clovis Oncology, including, but not limited to, the Investigator's Brochure, 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.

13.3 Patient Informed Consent

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

It is the responsibility of the investigator to obtain signed informed consent forms 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 informed consent form, 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 informed consent form consistent with the study protocol version used and approved by the relevant IEC/IRB. The informed consent form 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. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the informed consent form. A copy of the signed informed consent form will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

13.4 Study Monitoring

On behalf of Clovis Oncology, a CRO monitor will contact and visit the investigator at the study center prior to the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, 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 (i.e., the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file. Representatives from Clovis Oncology may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

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

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF must be completed, reviewed, signed, and dated by the principal investigator or co-investigator within a reasonable time period (<3 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

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

13.6 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, Clovis Oncology and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis Oncology 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.
- The sponsor discontinues the development of oral 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. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

13.7 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 Clovis Oncology. 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.

13.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and Clovis Oncology, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Clovis Oncology or its designees.

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 Clovis Oncology. 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 Clovis Oncology. Should the investigator wish to assign the study records to another party or move them to another location, Clovis Oncology must be notified in writing of the new responsible person and/or the new location. Clovis Oncology 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.

13.9 Clinical Study Report

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

13.10 Study Publication

All data generated from this study are the property of Clovis Oncology and shall be held in strict confidence along with all information furnished by Clovis Oncology. 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 Clovis Oncology. Written permission to the investigator will be contingent on the review by Clovis Oncology of the statistical analysis and manuscript, and will provide for nondisclosure of Clovis Oncology confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by Clovis Oncology. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authority from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

14 REFERENCES

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15 APPENDICES

Appendix A. Response Evaluation Criteria in Solid Tumors Criteria

Appendix B. Eastern Cooperative Oncology Group Performance Status Scale

Appendix C. Examples of Concomitant Medications that can Prolong the QT Interval

Appendix D. Examples of CYP Substrates with Narrow Therapeutic Range

Appendix A
Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[27] 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 one 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 two lesions per organ and five 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.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one 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 (Patients with Target (+/–Non-target) Disease.			
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
NE = Not evaluable.			

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 CR status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10. If an initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4-6 weeks later. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 6–8 weeks.

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

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 B
Eastern Cooperative Oncology Group Performance Status Scale

ECOG Performance Status[30]	
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 (e.g., 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[31] scale, the following conversion chart applies.[32]

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 no imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

Appendix C
Examples of Concomitant Medications that can Prolong the QT Interval

Generic Name	Class/Clinical Use	Comments
Arsenic trioxide	Anticancer/Leukemia	
Amitriptyline	Tricyclic Antidepressant	
Bepridil	Antianginal/heart pain	Females > Males
Chlorpromazine	Antipsychotic/Antiemetic/ schizophrenia/nausea	
Cisapride	GI stimulant/heartburn	Restricted availability; Females > Males
Clarithromycin	Antibiotic/bacterial infection	
Clomipramine	Tricyclic Antidepressant	
Desipramine	Tricyclic Antidepressant	
Disopyramide	Antiarrhythmic/abnormal heart rhythm	Females > Males
Dofetilide	Antiarrhythmic/abnormal heart rhythm	
Dolasetron	Antinausea/nausea, vomiting	Requires additional ECG monitoring (Part 1)
Domperidone	Antinausea/nausea, vomiting; prokinetic; lactation stimulation	Requires additional ECG monitoring (Part 1)
Doxepin	Tricyclic Antidepressant	
Droperidol	Sedative; Antinausea/anesthesia adjunct, nausea	Requires additional ECG monitoring (Part 1)
Erythromycin	Antibiotic; GI stimulant/bacterial infection; increase GI motility	Females > Males
Felbamate	Anticonvulsant/seizure	

Generic Name	Class/Clinical Use	Comments
Flecainide	Antiarrhythmic/abnormal heart rhythm	
Fluoxetine	Antidepressant/depression	
Foscarnet	Antiviral/HIV infection	
Fosphenytoin	Anticonvulsant/seizure	
Gatifloxacin	Antibiotic/bacterial infection	
Halofantrine	Antimalarial/malaria infection	Females > Males
Haloperidol	Antipsychotic/schizophrenia, agitation	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation, and torsades increases
Ibutilide	Antiarrhythmic/abnormal heart rhythm	Females > Males
Indapamide	Diuretic/stimulate urine and salt loss	
Isradipine	Antihypertensive/high blood pressure	
Levofloxacin	Antibiotic/bacterial infection	
Levomethadyl	Opiate agonist/pain control, narcotic dependence	
Mesoridazine	Antipsychotic/schizophrenia	
Methadone	Opiate agonist/pain control, narcotic dependence	
Metoclopramide	Antinausea/nausea, vomiting; diabetic gastroparesis; gastroesophageal reflux	Requires additional ECG monitoring (Part 1)
Moexipril/HCTZ	Antihypertensive/high blood pressure	
Moxifloxacin	Antibiotic/bacterial infection	

Generic Name	Class/Clinical Use	Comments
Naratriptan	Serotonin receptor agonist/Migraine treatment	
Nicardipine	Antihypertensive/high blood pressure	
Octreotide	Endocrine/acromegaly, carcinoid diarrhea	
Odansetron	Antinausea/Antiemetic	Requires additional ECG monitoring (Part 1)
Paroxetine	Antidepressant/depression	
Pentamidine	Anti-infective/pneumocystis pneumonia	Females > Males
Pimozide	Antipsychotic/Tourette's tics	Females > Males
Procainamide	Antiarrhythmic/abnormal heart rhythm	
Quetiapine	Antipsychotic/schizophrenia	
Quinidine	Antiarrhythmic/abnormal heart rhythm	Females > Males
Ranolazine	Chronic angina	
Risperidone	Antipsychotic/schizophrenia	
Roxithromycin	Antibiotic/bacterial infection	
Salmeterol	Sympathomimetic/asthma, COPD	
Sertraline	Antidepressant/depression	
Sotalol	Antiarrhythmic/abnormal heart rhythm	Females > Males
Sparfloxacin	Antibiotic/bacterial infection	

Generic Name	Class/Clinical Use	Comments
Sumatriptan	Serotonin receptor agonist/Migraine treatment	
Tacrolimus	Immunosuppressant/Immune suppression	
Tamoxifen	Anticancer/breast cancer	
Thioridazine	Antipsychotic/schizophrenia	
Tizanidine	Muscle relaxant	
Venlafaxine	Antidepressant/depression	
Ziprasidone	Antipsychotic/schizophrenia	
Zolmitriptan	Migraine treatment	

Refer to https://crediblemeds.org/.

Appendix D
Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range[a]	
CYP2C9	Warfarin, phenytoin	
CYP2C19	S-mephenytoin	
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine	

The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012.[22]

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