A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Protocol Number:	CO-338-014
Investigational Product:	Rucaparib (CO-338)
Eudra CT Number:	[redacted]
IND Number:	[redacted]
Development Phase:	Phase 3
Indications Studied:	Platinum-sensitive, high-grade serous and endometrioid epithelial ovarian, primary peritoneal, and fallopian tube cancer
Sponsor Name and Address:	Clovis Oncology, Inc. [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 Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines ICH E6(R2). Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	[redacted]
[redacted]	[redacted]
Amendment 5 Date:	06 July 2020

CONFIDENTIALITY STATEMENT

Coordinating Investigators for the Study

Coordinating Investigator for North America:

[redacted]

Coordinating Investigator for Europe, Middle East, and Asia Pacific:

[redacted]

Protocol Approval Signature Page

Protocol:	CO-338-014
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Date:	06 July 2020
Amendment:	5

[redacted]

[redacted]

Protocol Acceptance Form

Protocol:	CO-338-014
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I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

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

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1 SYNOPSIS

Protocol Number	CO-338-014
Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Study Phase	Phase 3
Introduction	Rucaparib is an orally available, small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1, PARP-2, and PARP-3 and is being developed for treatment of ovarian cancer associated with homologous recombination deoxyribonucleic acid (DNA) repair deficiency. The safety and efficacy of rucaparib has been evaluated in several Phase 1, Phase 2, and Phase 3 studies. Rucaparib (Rubraca®) is approved in the United States (US) as monotherapy treatment for adult patients with deleterious breast cancer gene (BRCA) mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with 2 or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who have a complete or partial response to platinum-based chemotherapy.[1] Rucaparib is also approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy, and for maintenance treatment of adult patients with platinum-sensitive recurrent EOC, FTC, or PPC who are in response (complete or partial) to platinum-based chemotherapy.[2] Normal cells repair single-strand breaks (SSBs) in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP-1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer gene 1 and 2 (BRCA1 and BRCA2), as well as many others. Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes in high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patients with HGSOC have homologous recombination deficiency (HRD).[3] Drivers of HRD include: 1. Germline mutations in the BRCA1 and BRCA2 genes (gBRCA). These are the strongest known hereditary factors for EOC, accounting for up to 15% of all EOC.[4, 5] 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”). 2. Somatic BRCA1/2 mutations (sBRCA) (6 – 8% of HGSOC patients)[3, 6] 3. Mutation in a homologous recombination gene other than BRCA1/2 (approximately 16% of HGSOC patients).[3] Nonclinical studies by several

groups have identified RAD proteins (eg, RAD51, RAD51C, RAD52, RAD54L),[7-10] Fanconi Anemia proteins (eg, FANCA, FANCC, FANCD2),[11-13] and many others (eg, ATM, ATR, CHEK1, CHEK2)[14-17] as being involved in homologous recombination.

4. Functional silencing of homologous recombination genes, such as through BRCA1 promoter methylation (approximately 10% of HGSOC patients)[3] or other mechanisms

Inhibition of DNA damage repair in cancer cells, which are intrinsically genetically unstable, represents an attractive opportunity for the development of new therapies. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect, whereas inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. Normal cells, with only one DNA repair pathway affected by inhibition of PARP, still have an intact DNA repair pathway that can compensate, whereas cancer cells with pre-existing HRD that are treated with a PARP inhibitor develop critically DNA repair deficiency and enter apoptosis. This concept of synthetic lethality has been demonstrated in landmark in vitro and in vivo studies[18, 19] as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer with or without an associated germline BRCA mutation.[20-26] In vitro studies have also shown that cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity.[27-30] It is possible that the 24% overall response rate (ORR) observed in olaparib-treated ovarian cancer patients without evidence of a gBRCA1/2 mutation[23] was due to HRD driven by a sBRCA1/2 mutation or by an alteration in another key homologous recombination gene.

Clinical activity in HGSOC has also been observed with switch maintenance PARP inhibitor therapy following response to platinum-based chemotherapy. Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median progression-free survival (PFS) (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio (HR) of 0.35 (95% confidence interval [CI], 0.25 – 0.49).[31] Patients with a BRCA mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[32] It should be noted that the outcomes of sBRCA + gBRCA mutant patients were the same as gBRCA mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a BRCA mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$), suggesting that patients with DNA repair defects in genes other than BRCA are likely contributing to the overall PFS result.[32]

The purpose of this study is to evaluate PFS of patients with platinum-sensitive, relapsed high-grade EOC, FTC, or PPC who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy. Prior to final analysis, patients will be placed into molecularly defined subgroups of HRD based on the Final Clinical Trial Assay (FCTA). It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD.

Study Overview	This is a randomized, international, double-blind, placebo-controlled Phase 3 study evaluating rucaparib maintenance therapy in advanced ovarian cancer. The primary endpoint is PFS by Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1[33] as assessed by the investigator. Risk/benefit will be assessed regularly by an Independent Data Monitoring Committee (IDMC) that will have access to unblinded datasets. This study will enroll patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or FTC who achieved either a complete response (CR) by RECIST v1.1 or a partial response (PR), defined as either a RECIST v1.1 PR or a cancer antigen 125 (CA-125) response by Gynecologic Cancer Intergroup (GCIG) criteria,[34] to their last platinum-based regimen. All responses will require CA-125 that is within the upper limit of normal (ULN). During the screening phase, each patient will have archival tumor tissue analyzed for mutations in homologous recombination pathway genes. Genes of interest will be sequenced using Foundation Medicine's next generation sequencing (NGS) test, which examines a panel of cancer-related genes, including BRCA1/2 and other homologous recombination pathway genes. Patients will be stratified into one of three HRD subgroups (BRCA1/2 mutation in tumor tissue [tBRCA], HRD due to mutation in a homologous recombination gene other than BRCA1/2 [nonBRCA HRD (nbHRD)], or biomarker negative) for randomization based on the results obtained with Foundation Medicine's Initial Clinical Trial Assay (ICTA) (Appendix A). Enrollment of patients known *a priori* to harbor a gBRCA mutation classified as deleterious (pathogenic), suspected deleterious, or equivalent, on the most recent assessment, will be limited to 150. Enrollment of patients with a BRCA gene mutation detected in tumor tissue (tBRCA), including those known to harbor a gBRCA mutation, will be limited to 200. Once this cap is reached, newly screened patients identified as having a BRCA mutation in tumor tissue will be offered treatment in another study. The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Tumor tissue results for the BRCA genes will be provided to patients who consent to receive this information upon availability. Results for the remainder of the gene panel will be provided to consenting patients upon study treatment discontinuation. Results are to be disclosed to consenting patients by the study physician as part of an overall clinical discussion. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline BRCA testing, this result will be entered into the clinical trial database. Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. Tumor DNA will also be assessed by the NGS test to detect the presence of genomic scars.[35-38] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). The extent of genomic scarring and its utility in predicting clinical outcome with rucaparib will

	be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study, but will be completed earlier. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 study. The FCTA analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the primary efficacy analysis. The sponsor will remain blinded to all tumor tissue and germline test results until the primary efficacy analysis is conducted.
Number of Patients	Approximately 540 patients will be enrolled. A minimum of 180 and a maximum of 200 patients with a deleterious tBRCA mutation will be enrolled. Enrollment of patients with a known deleterious gBRCA mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.
Number of Sites	This is a multicenter, multinational study. Patients will be enrolled from approximately 90 – 100 study sites.
Study Duration	Q4 2013 – Q2 2022 (estimated last patient, last visit [LPLV])
Study Objectives	The primary objective of this study is: • To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups The secondary objectives of this study are: • To evaluate patient-reported outcome (PRO) of disease-related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18) • To evaluate PRO utilizing the complete FOSI-18 • To evaluate survival benefit • To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups • To evaluate safety • To determine the population pharmacokinetics (PK) of rucaparib The exploratory objectives of this study are: • To evaluate the relationship between CA-125 levels and disease progression as assessed by investigator (invPFS) • To evaluate PFS2 (PFS on the subsequent line of treatment) • To evaluate ORR • To evaluate duration of response (DOR) • To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D) • To explore the relationship between rucaparib exposure, efficacy, and safety
Study Population	**Inclusion Criteria** All patients enrolling into the study must meet all of the following inclusion criteria: 1. Have signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-specific

	evaluation 2. Be ≥18 years of age at the time the informed consent form is signed 3. Have a histologically confirmed diagnosis of high-grade (Grade 2 or 3) 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 – Grade 2 tumors classified under a 3-tier system should be re-reviewed by local pathology and confirmed as high-grade under the 2-tier system 4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e. documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered) – Received ≥2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will not be counted as a non-platinum regimen. – There is no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered. – If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen – Prior maintenance therapy following a prior treatment regimen is permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anticancer therapy is permitted to be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial. 5. Achieved best response of either CR or PR to the most recent platinum-based regimen administered and is randomized to study treatment within 8 weeks of the last dose of platinum received. – The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the 2nd chemotherapy agent is per investigator's discretion. – A minimum of 4 cycles of platinum chemotherapy must have been administered. There is no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of therapy for the specific purpose of enabling patient eligibility and randomization within 8 weeks of the last platinum dose is not permitted. – A CR is defined as a complete radiologic response per RECIST v1.1, i.e. absence of any detectable disease and CA-125 <ULN.* – A PR is defined as either a partial response per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serologic response per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1).* o CA-125 must also be <ULN for all responses classified as a PR

	– R0 surgery (no visible tumor) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen is <u>not</u> permitted. The response assessment must be determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 > 2 x ULN <u>immediately</u> prior to the chemotherapy regimen is required. – Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study. – All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record 6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 to 12 x 10 µm sections, or equivalent) available for planned analyses. – The <u>most recently</u> collected tumor tissue should be provided, if available – Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample. – Sample must be received at the central laboratory **<u>at least 3 weeks prior to start of treatment</u>** in order to enable stratification for randomization 7. Have CA-125 measurement that is < ULN 8. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug: – Bone Marrow Function o Absolute neutrophil count (ANC) ≥ 1.5×10^9/L o Platelets > 100×10^9/L o Hemoglobin ≥ 9 g/dL – Hepatic Function o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN o Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome) – Renal Function o Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula * <u>Note</u>: It is acceptable for sites to utilize local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it is not a requirement to re-read radiological scans to collect this data.

	Exclusion Criteria Patients will be excluded from participation if any of the following criteria apply: 1. History of a prior malignancy except: – Curatively treated non-melanoma skin cancer – Breast cancer treated curatively > 3 years ago, or other solid tumor treated curatively > 5 years ago, without evidence of recurrence – Synchronous endometrioid endometrial cancer (Stage 1A G1/G2) 2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible. 3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study 4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks. 5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study drug 6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C 7. Pregnant or breast feeding. Women of child-bearing potential must have a negative serum pregnancy test ≤ 3 days prior to first dose of study drug. 8. 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 study drug and/or ongoing adverse effects from such treatment > NCI-CTCAE Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug – Ongoing hormonal treatment for previously treated breast cancer is permitted – Refer also to inclusion criteria #4 for guidelines pertaining to prior maintenance therapy 9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤ 7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F) 10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration 11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study Pregnancy is an exclusion criterion and women of child-bearing potential must not be considering getting pregnant during the study. Female patients of reproductive potential must practice a highly effective method

	of contraception (failure rate < 1% per year) with their male partners during treatment and for 6 months following the last study drug dose. No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolled into the study.
Study Treatment	Eligible patients will be randomized 2:1 to receive rucaparib (600 mg twice a day [BID]) or placebo. Randomization will occur by a central randomization procedure using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced: • HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A). • Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment • Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN. Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study drug will be taken orally twice daily (12 hours apart) with at least 8 oz (240 mL) of water. Study drug may be taken with an empty stomach or with food. Patients will take study drug twice daily for continuous 28-day cycles until disease progression by RECIST as assessed by the investigator, or other reason for discontinuation. Treatment interruptions and/or dose reductions are permitted in the event of unacceptable toxicity.
Withdrawal Criteria	A patient must be discontinued from treatment with study drug if any of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative • Progression of patient's underlying disease by RECIST as assessed by the investigator • 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
Disease Assessments for Efficacy	Efficacy measures will include clinical examination, CA-125 measurement, and appropriate imaging (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. Disease assessment will be performed at screening, at the end of every 12 calendar weeks after start of treatment on Day 1 of Cycle 1, at discontinuation of treatment, and as clinically indicated Disease progression will be determined by RECIST (Appendix B). Patients with a CR at study entry will only be considered to have disease progression if a new

<table>
<tr><td></td><td>lesion is identified. Patients who meet GCIG CA-125 criteria (Appendix C) for disease progression should have a radiologic assessment by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST per the protocol schedule.
Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 1 week prior is permitted) until disease progression, as assessed by the investigator. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor’s medical monitor before decreasing frequency.</td></tr>
<tr><td>Safety Assessments</td><td>Safety assessments may include adverse events (AEs), hematology, serum chemistry, vital signs, body weight, concomitant medications/procedures, ECOG performance status (Appendix D), and study drug modifications. As of implementation of Protocol Amendment 5, AEs will be monitored but only serious adverse events (SAEs)/adverse events of special interest (AESIs) will be recorded in the eCRF. Ongoing SAEs and AESIs will be followed until resolution, stabilization, or lost to follow-up.</td></tr>
<tr><td>Statistical Procedures</td><td>Sample Size Justification
The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious tBRCA mutation will be enrolled. Enrollment of patients with a known deleterious gBRCA mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA that will evaluate homologous recombination gene mutations and/or extent of genomic scarring in tumor tissue.
The table below provides estimated sample sizes and power calculations.
<table>
<tr><th>Group</th><th>Hazard Ratio</th><th>Cumulative N</th><th>Minimum Number of Events (70%)</th><th>Median PFS Placebo vs Rucaparib (months)</th><th>Power</th><th>One-sided Alpha</th></tr>
<tr><td>tBRCA</td><td>0.50</td><td>180</td><td>126</td><td>6 vs 12</td><td>90%</td><td>0.025</td></tr>
<tr><td>All HRD (tBRCA + nbHRD)</td><td>0.60</td><td>300</td><td>210</td><td>6 vs 10</td><td>90%</td><td>0.025</td></tr>
<tr><td>ITT Population (tBRCA + nbHRD + Biomarker Negative)</td><td>0.70</td><td>540</td><td>378</td><td>6 vs 8.5</td><td>90%</td><td>0.025</td></tr>
</table>
Analysis Populations
Safety: The safety population will consist of all patients who received at least one dose of protocol-specified treatment.
Intent-to-treat (ITT): The ITT population will consist of all randomized patients.</td></tr>
</table>

	Response evaluable: The response evaluable population will consist of all patients who have measurable or evaluable disease at study entry, received at least one dose of study drug, and who had at least one post-baseline disease assessment. **General Statistical Considerations** Quantitative variables will be summarized using descriptive statistics. For variables registered on a continuous scale, the following will be presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The primary and key secondary endpoints will be tested among the tBRCA subgroup, all HRD subgroup, and all randomized patients, using an ordered step-down multiple comparisons procedure. Investigator-determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant, then invPFS will be tested in the all HRD subgroup followed by invPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the DRS-P subscale of the FOSI-18 will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure. PFS by IRR will be evaluated as a stand-alone secondary endpoint. <u>Primary Efficacy Analysis</u> The primary efficacy analysis for the study is investigator-determined PFS (invPFS) by RECIST. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or death due to any cause, whichever occurs first. The stratification factors included in the primary analysis of invPFS will be HRD classification (tBRCA, nbHRD or biomarker negative), interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment, and best response to the most recent platinum-based regimen (either CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN. Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly defined subgroups) can be assessed prospectively. <u>Secondary Efficacy Analyses</u> Secondary efficacy endpoints include: • PRO of disease-related symptoms as measured by the DRS-P subscale score of the FOSI-18 • PRO as measured by the total score of the FOSI-18 • Overall survival (OS)

	• PFS by RECIST v1.1 as assessed by IRR The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS–P subscale score. Similarly, an event in worsening of PRO utilizing the FOSI-18 total score will be defined as the time from randomization to an 8-point reduction in the total score. OS, time to death from any cause, is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive. PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first. <u>Safety Analysis</u> Data from all patients who receive at least one dose of study drug will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. AEs will be summarized overall, with separate summaries for SAEs, AEs leading to treatment discontinuation or death, and CTCAE Grade 3 or higher AEs. **Independent Data Monitoring Committee (IDMC)** No formal efficacy interim analyses for early stopping are planned. An IDMC will meet regularly to review the efficacy and safety data from this study. The IDMC will: • Review efficacy and safety of rucaparib compared to placebo to ensure the study is beneficial to patients; • Ensure the study is conducted in a high quality manner; and • Monitor the size of the tBRCA subgroup and known gBRCA subgroup The IDMC will hold meetings and continue to review data until the protocol-specified primary endpoint collection is complete (i.e., 70% of the patients in the tBRCA subgroup have an event of PFS) and the IDMC recommend the sponsor to unblind the treatment assignments for assessment of primary efficacy. The treatment assignment was unblinded in June 2017 for the primary efficacy analysis and thus no further IDMC meetings are planned.

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
ALCOA+	attributable, legible, contemporaneous, original, and accurate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration curve
AUCR	ratio of the area under the curve
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice a day
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BUN	blood urea nitrogen
CA-125	cancer antigen 125
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.03)
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
DRS−P	disease-related symptoms−physical

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EQ-5D	Euro-Quality of Life 5D
EU	European Union
FCTA	Final Clinical Trial Assay
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOSI-18	FACT-Ovarian Symptom Index 18
FSH	follicle-stimulating hormone
FTC	fallopian tube cancer
GALT	gut-associated lymphoid tissue
gBRCA	germline BRCA
$gBRCA^{mut}$	deleterious germline BRCA mutation
$BRCA^{wt}$	wild-type BRCA
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
h	Hour
Hct	Hematocrit
HDL	high-density lipoprotein
H&E	hematoxylin and eosin
hERG	human ether-a-go-go-related gene
Hgb	hemoglobin
HGSOC	high grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio
HRD	homologous recombination deficiency
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
ICTA	Initial Clinical Trial Assay

IC_{xx}	concentration where maximum response is inhibited by XX%
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
invPFS	disease progression according to RECIST v1.1 as assessed by the investigator, or death from any cause
IRB	Institutional Review Board
IRR	independent radiology review
irrPFS	disease progression according to RECIST v1.1 as assessed by independent radiology review, or death from any cause
ITT	Intent-to-treat
IV	intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDL	low-density lipoprotein
LOH	loss of heterozygosity
LPLV	last patient, last visit
MATE	multidrug and toxin extrusion transporter
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	minute
MRI	magnetic resonance imaging
mut	mutant
nbHRD	non-BRCA homologous recombination deficiency
NCCN-FACT	National Comprehensive Cancer Network-Functional Assessment of Cancer
NCI	National Cancer Institute
NGS	next generation sequencing
NOAEL	no-observed-adverse-effect level
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PLD	PEGylated liposomal doxorubicin
PFS	progression-free survival
PFS2	second event of progression-free survival

P-gp	P-glycoprotein
PID	poly (adenosine diphosphate [ADP]-ribose) polymerase inhibiting dose
PIS	patient information sheet
PK	pharmacokinetic(s)
PPC	primary peritoneal cancer
PR	partial response
PRO	patient-reported outcome
PS	performance status
QD	once a day
QoL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAS	statistical analysis software
sBRCA	somatic breast cancer gene 1 or 2 mutation
SD	stable disease
SNP	single-nucleotide polymorphism
SOC	system organ class
SOP	Standard operating procedure
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
tBRCA	tumor tissue alteration in BRCA1 or BRCA2, includes gBRCA and sBRCA
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse events
T_{max}	time to maximum concentration
UGT	uridinediphosphate-glucuronosyletransferase
ULN	upper limit of normal
unk	unknown
UV	ultraviolet
US	United States
v	version
VEGF	Vascular endothelial growth factor
WBC	white blood cell
WOCBP	women of child-bearing potential
WT	wild type

3 INTRODUCTION

3.1 Ovarian Cancer

3.1.1 General Overview

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[39, 40] After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy.[41] Relapse still occurs, however, in the majority of cases, and only 10–30% of women experience long-term survival.[41] Advanced stage disease is associated with a 5-year survival rate of only 30–40%.[39]

Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade.[41] The site of origin of epithelial ovarian cancer (EOC) remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium;[42, 43] however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[41, 44] EOC, PPC and fallopian tube cancer (FTC) behave very similarly, and are therefore treated in the same way.

The median age at presentation of EOC is 60 years. Many women present with advanced disease and therefore have a poor prognosis.

3.1.2 Treatment of Ovarian Cancer

The standard approach to treatment of advanced ovarian cancer is cytoreductive surgery (either at time of diagnosis or interval debulking following 2 – 3 cycles of neoadjuvant chemotherapy), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to eight cycles of platinum- and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after three or four cycles of primary chemotherapy, followed by three further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with deoxyribonucleic acid (DNA).[45, 46]

The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. As many patients experience multiple relapses, prognosis and response to therapy decreases as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to platinum-based therapy.

Platinum-based regimens dominate ovarian cancer therapy and define treatment groups.[46] In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease;

and patients whose disease relapses more than 6 months after the last platinum-based therapy was administered are considered to have platinum-sensitive disease. These classifications are clinical, and not based on a mechanistic definition of platinum sensitivity or resistance.

PARP inhibitor monotherapy has elicited objective responses in patients with platinum-sensitive disease as well as in patients with platinum-resistant disease, although response rates are higher in the former population.[23-25] This indicates that using platinum-sensitivity alone as a selection marker for PARP inhibitor therapy is not a very effective tool, although it is a reasonable place to begin predictive biomarker development.

Maintenance therapy following a response to standard treatment provides an opportunity to extend the disease-free period. Maintenance strategies evaluated to date for ovarian cancer have focused on the prolonged use of single-agent chemotherapy, antiangiogenesis agents, hormonal therapy, vaccines, and intraperitoneal chemotherapy. The OCEANS study evaluated carboplatin and gemcitabine with or without bevacizumab as part of the initial treatment and then as maintenance in women with platinum-sensitive ovarian, primary peritoneal, or FTC who were in their first relapse following primary chemotherapy. The addition of bevacizumab resulted in a statistically significant improvement in progression-free survival (PFS) (median 12.4 vs 8.4 months; HR=0.484 [95% CI, 0.388 to 0.605; log-rank $P<0.00001$]).[47] The PFS benefit of bevacizumab administered together with chemotherapy followed by single agent bevacizumab maintenance treatment compared to chemotherapy alone and placebo maintenance was further established in two front-line Phase 3 studies, GOG-218 (HR=0.717 [95% CI, 0.625 to 0.824; log-rank $P<0.001$])[48] and ICON-7 (HR=0.81 [95% CI, 0.70 to 0.94; log-rank $P<0.04$]).[49] Based on these trials, the European Medicines Agency (EMA) approved bevacizumab, in combination with carboplatin and paclitaxel, for front-line treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III B, III C and IV) epithelial ovarian, fallopian-tube, or primary peritoneal cancer, and, in combination with carboplatin and gemcitabine, for treatment of first recurrence of platinum-sensitive epithelial ovarian, fallopian-tube or primary peritoneal cancer in women who have not received prior therapy with bevacizumab or other vascular-endothelial-growth-factor (VEGF) inhibitors or VEGF-receptor-targeted agents.

3.1.3 Homologous Recombination Deficiency

DNA is constantly damaged by both endogenous and exogenous (environmental) assaults. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs). 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.

Normal cells repair SSBs in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of DSBs, which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer gene 1 and 2 (BRCA1 and BRCA2), among others.

If either the BER or homologous recombination pathway is rendered non-functional, the remaining functional pathway can compensate to ensure ongoing DNA repair and cell cycling. For example, when the BRCA-associated homologous recombination pathway is lost or dysfunctional, repair shifts towards the BER repair pathway that is dependent on PARP enzymes. In contrast, in the setting in which both repair pathways (BER and homologous recombination) are rendered non-functional, the cell dies. This concept, where a defect in either of two pathways can be withstood by a cell, but defects in both are lethal, is referred to as synthetic lethality. This type of lethality can arise from a variety of different interactions. In the case of DNA damage repair, dual non-functionality can be achieved by enzymatic inhibition of PARP in the context of a genetic mutation in the BRCA1 or BRCA2 genes.

Synthetic lethality has been demonstrated in landmark in vitro and in vivo studies as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer. Bryant and colleagues showed that cell lines and a tumor xenograft deficient in homologous recombination (via a defect in a BRCA or other homologous recombination gene) were highly sensitive to PARP inhibition.[18] This study also showed that synthetic lethality could be achieved regardless of whether the mutation was in BRCA1 or BRCA2. In a parallel set of experiments, Farmer and colleagues illustrated that chemical inhibition of PARP1 was more potent in homozygous BRCA-deficient cell lines than in heterozygous mutant or wild-type cell lines.[19] These findings were also supported by a BRCA2-deficient murine model. Taken together, these studies provided support for the treatment of patients with a BRCA-deficient tumor with a PARP inhibitor.

3.1.4 Role of HRD in Ovarian Cancer

Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes associated with high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patient with HGSOC have homologous recombination deficiency (HRD).[3] Drivers of HRD in ovarian cancer include:

1. Germline mutations in the BRCA1 and BRCA2 genes (gBRCA). These are the strongest known hereditary factors for EOC, accounting for up to 15% of all EOC.[4, 5] 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”).

2. Somatic BRCA1/2 mutations (sBRCA) (approximately 6 – 8% of HGSOC patients)[3, 6]

3. Mutation in a homologous recombination gene other than BRCA1/2 (approximately 16% of HGSOC patients).[3] Nonclinical studies by several groups have identified RAD proteins (eg, RAD51, RAD51C, RAD52, RAD54L),[7-10] Fanconi Anemia proteins (eg, FANCA, FANCC, FANCD2),[11-13] and many others (eg, ATM, ATR, CHEK1, CHEK2)[14-17] as being involved in homologous recombination.

4. Functional silencing of homologous recombination genes, such as through BRCA1 promoter methylation (approximately 10% of HGSOC patients)[3] or other mechanisms

Mutations in the BRCA genes in the tumor can be detected through next-generation sequencing (NGS). A possible approach to identify non-BRCA patients with HRD is to detect genomic scars within the tumor, which arise from the use of error-prone DNA repair pathways when HRR is compromised. Through a series of experiments and data analyses, the sponsor has determined that a potential method for identifying patients who may be sensitive to rucaparib is to assess genomic scarring by quantifying the extent of loss of heterozygosity across the tumor genome (tumor genomic loss of heterozygosity [LOH]). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms, which include both known (i.e. BRCA mutations) and unknown genomic mechanisms.[35, 38]

3.2 PARP Inhibitors

Please refer to the current Investigator's Brochure for comprehensive information on rucaparib.

PARP inhibitors have been evaluated in the clinic for the past decade. Olaparib (AZD-2281), the most advanced investigational PARP inhibitor, has demonstrated compelling Phase 2 clinical activity, both in treatment and maintenance settings, in relapsed, HGSOC patients (both germline BRCA mutant and wild-type) and in metastatic breast cancer patients with a gBRCA mutation. The concept of synthetic lethality was exploited in two proof-of-concept clinical studies with olaparib in patients with BRCA-associated tumor types. These studies evaluated the efficacy and safety of continuous oral dosing with olaparib in women with either relapsed ovarian cancer or advanced breast cancer and a gBRCA mutation.[21, 22] In these patients, who had received a median of three prior chemotherapy regimens, encouraging overall response rates of 33% and 41%, were observed, in gBRCA ovarian and gBRCA breast cancer, respectively. In a third study, olaparib treatment was associated with a greater overall response rate (ORR) in patients with gBRCA-associated ovarian cancer compared with the patients in the non-gBRCA associated cohort (41% vs 24%, respectively).[23] In a fourth study that evaluated olaparib versus PEGylated liposomal doxorubicin (PLD) in patients with a gBRCA mutation and relapsed ovarian cancer, the efficacy of olaparib was consistent with that observed in previous studies.[24]

Activity in HGSOC has also been observed with PARP inhibitor switch maintenance therapy following response to platinum-based chemotherapy.[31, 32] Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio of 0.35 (95% CI, 0.25 – 0.49).[31] Patients with a BRCA mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[32] It should be noted that the outcomes of sBRCA + gBRCA mutant patients were the same as gBRCA mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a BRCA mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$).[32]

Niraparib (MK-4827) has exhibited clinical activity in a Phase 1 study in both BRCA-mutated ovarian cancer (8 RECIST PRs) and sporadic ovarian cancer (5 RECIST PRs and/or GCIG

CA-125 responses).[25] In a Phase 1 evaluation of BMN 673, 11 of 17 BRCA-mutated ovarian cancer patients treated at doses ≥100 µg/day exhibited a RECIST and/or CA-125 response.[26]

Taken together, these data support the potential role for the PARP inhibitor rucaparib in the treatment of patients with BRCA-associated ovarian cancer. Furthermore, the 24% ORR and HR of 0.53 in the non-BRCA cohorts described above[23, 32] suggests that the clinical utility of PARP inhibitors can be extended to a larger patient group. Patients with HRD due to defects in homologous recombination genes other than BRCA, i.e. nbHRD, may be part of this larger group.

3.3 Rucaparib

Rucaparib (formerly known as AG-014447 and PF-01367338) refers to the free base. The camphorsulfonic acid salt form (also referred to as camsylate salt) CO-338 (formerly known as PF-01367338-BW) will be used in this clinical trial.

Rucaparib (Rubraca®) is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3 approved in the United States (US) as monotherapy treatment for adult patients with deleterious BRCA mutation (germline and/or somatic)-associated EOC, FTC, or PPC cancer who have been treated with 2 or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who have a complete or partial response to platinum-based chemotherapy.[1] Rucaparib is also approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy, and for maintenance treatment of adult patients with platinum-sensitive recurrent EOC, FTC, or PPC who are in response (complete or partial) to platinum-based chemotherapy.[2]

Nonclinical evaluation has demonstrated exquisite sensitivity of BRCA1 and BRCA2 homozygous mutant cell lines to rucaparib and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary deficiencies of BRCA1 and/or BRCA2. Rucaparib has also shown antitumor activity as a single agent in the MDA-MB-436 (BRCA1 mutant) xenograft mouse model. The activity of rucaparib in these nonclinical experiments was similar to that of olaparib.

Comprehensive nonclinical and clinical information for rucaparib is available in the current Investigator's Brochure.

3.3.1 Nonclinical Experience

3.3.1.1 Rucaparib Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics (PK) and toxicokinetics of rucaparib (as camsylate salt) following oral administration, 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.

In vitro plasma protein binding studies in mouse, rat, and dog plasma showed moderate binding and ranged from 49.5% to 73%. Plasma protein binding in humans ranged from 55% to 75%.

Recombinant cytochrome P450 (CYP) studies indicated that CYP2D6, and to a lesser extent, CYP1A2 and CYP3A4, have the ability to metabolize rucaparib.

In vitro studies indicated that rucaparib reversibly inhibited (in order of decreasing potency) CYP1A2, CYP2C19, CYP2C9, CYP3A, CYP2C8, and CYP2D6. Rucaparib demonstrated concentration-dependent induction of CYP1A2 and down-regulation of CYP3A4 and CYP2B6 at clinically relevant concentrations in a hepatocyte incubation study. No time-dependent CYP inhibition was observed. Rucaparib also moderately inhibited uridinediphosphate-glucuronosyletransferase (UGT)1A1. 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 twice a day [BID]) using the mechanistic static modeling.[50, 51] 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, downregulation could further increase AUCR for CYP3A and result in elevated exposures of drugs that are CYP3A substrates.

Rucaparib is a substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro data indicate rucaparib is a potent inhibitor of multidrug and toxin extrusion transporter (MATE)-1 and MATE2-K (efflux transporters on renal tubule cells), and moderate inhibitor of organic cation transporter (OCT)1, BCRP, and P-gp.

Quantitative whole body autoradiography studies in Long Evans rats showed [^{14}C] rucaparib radioequivalents were rapidly and widely distributed to tissues following IV administration, consistent with a large volume of distribution. At 2 minutes after dosing, highest concentrations were found in kidney, lung, thyroid gland, heart, stomach mucosa, liver adrenal glands, spleen, and blood. Little radioactivity was present in brain; levels were undetectable at 15 minutes 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.

3.3.1.2 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.

Rucaparib camsylate in capsules was also given orally to rats at doses of 10, 40, and 100 mg/kg/day for 91 consecutive days with a 28-day recovery period. Decreased body weight and body weight gain were observed for animals given ≥40 mg/kg/day. At the end of the recovery phase, mean body weight was still lower for males given 100 mg/kg/day and females given ≥40 mg/kg/day. Hematological findings included decreases in red blood cell mass parameters in animals given ≥40 mg/kg/day (which correlated with decreased bone marrow hypocellularity), and decreases in reticulocytes, white blood cells (WBC) and absolute lymphocytes at ≥40 mg/kg/day. The latter changes correlated with the microscopic findings of decreased lymphocytes in the mandibular lymph nodes and gut-associated lymphoid tissue. All effects were reversible. Microscopically, bone marrow hypocellularity at 100 mg/kg/day and minimally decreased lymphocytes in lymphoid tissues at ≥40 mg/kg/day were noted and were completely reversed at the end of the recovery period. The NOAEL was established to be 100 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.

3.3.1.3 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 (hERG) activity, the IC_{50} and IC_{20} for the inhibitory effects of rucaparib (50% inhibitory concentration and 20% inhibitory concentration) on hERG potassium currents were 24 µM (7761 ng/mL) and 7 µM (2264 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 maximum concentration [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.

3.3.2 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.

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

3.3.2.1 Rucaparib Monotherapy

3.3.2.1.1 Study CO-338-010

Clovis-sponsored study CO-338-010 is a 2-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Part 1 is a Phase 1 portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. The primary objective of Part 1 is to determine the optimal monotherapy dose for orally administered rucaparib. Part 2 is a Phase 2 portion in patients with platinum-sensitive relapsed ovarian cancer with evidence of a gBRCA mutation who have received at least 2, but no more than 4, prior regimens. The primary objective of Part 2 is to assess the overall objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Study CO-338-010 was initiated in Q4 2011. As of 27 June 2014, 56 patients (median age 50 yrs [range 21−71]; 51 female; 27 breast cancer, 20 ovarian/peritoneal cancer, 9 other tumor) were treated at dose levels of 40, 80, 160, 300, and 500 mg once daily (QD), and 240, 360, 480, 600, and 840 mg BID rucaparib administered continuously in the Phase 1 portion of the study. A total of 50 patients discontinued rucaparib; n=46 due to disease progression; n=2 due to an adverse event (AE) (unrelated to rucaparib); n=1 due to consent withdrawal; and n=1 due to an eligibility criteria violation. One of 6 patients treated with 360 mg BID rucaparib experienced a dose-limiting toxicity (DLT) of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 nausea despite maximal intervention in Cycle 1 of treatment. No DLTs were observed during Cycle 1 in the 480 (n=9), 600 (n=5), and 840 mg BID (n=3) cohorts; however, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1. The dose of 600 mg BID rucaparib was selected as the recommended dose for Phase 2 and Phase 3 studies based on the overall safety & tolerability, PK, and clinical activity profile. As of June 27, 2014, 15 patients (median age=58 [range=45-84]; 9 ECOG PS=0) with platinum-sensitive, relapsed

ovarian cancer associated with a deleterious BRCA1/2 mutation have been enrolled in the Phase 2 portion of the study. One patient has discontinued rucaparib due to disease progression.

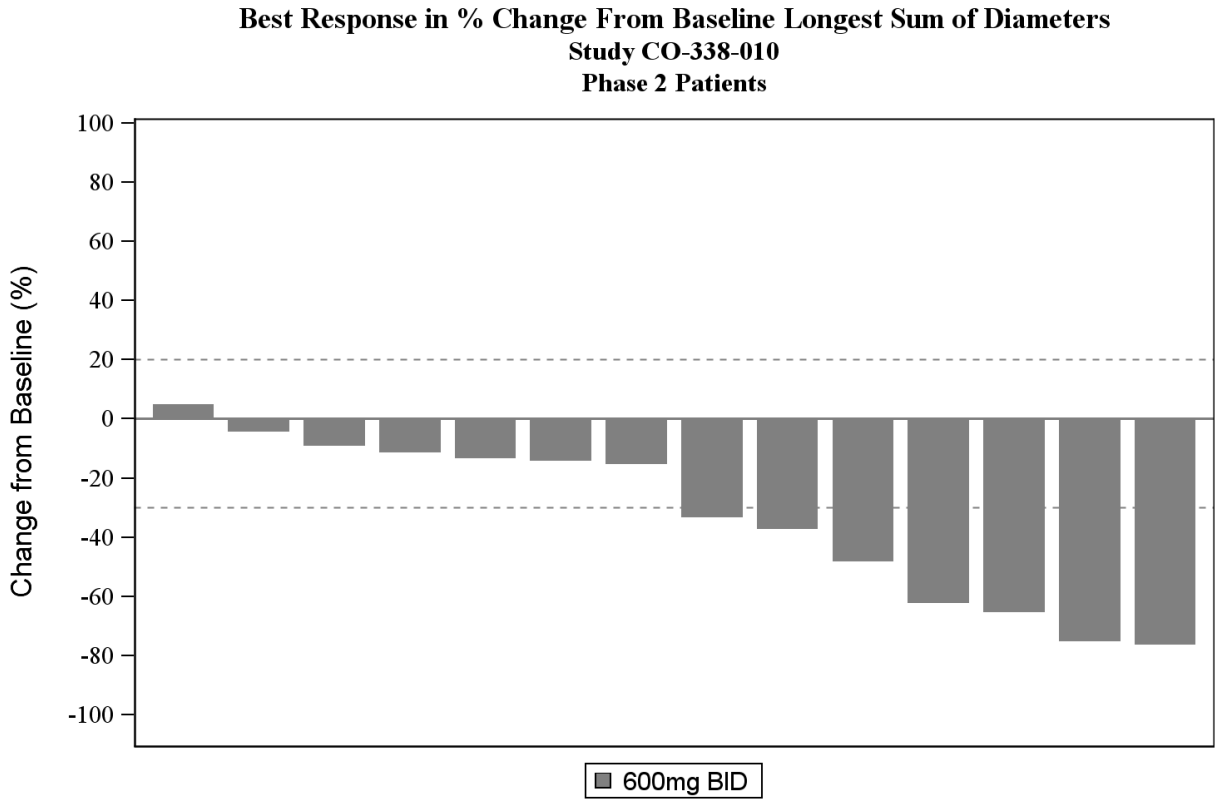
Treatment-related AEs (all grades) reported in ≥15% of patients treated with 600 mg BID rucaparib include gastrointestinal and related symptoms (nausea, vomiting, dysgeusia, diarrhea, abdominal pain, and decreased appetite), anemia, fatigue/asthenia, and headache. Elevations of alanine aminotransferase (ALT) and/or AST have been reported. The ALT/AST elevations occur early (within first 2-4 weeks of treatment), were generally mild to moderate (Gr 1-2), not accompanied by any changes in bilirubin levels, and often transient and resolved to within normal ranges, or stabilize. No patient met the laboratory criteria for Hy's Law.[52] As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. All treatment-related AEs were successfully managed with concomitant medication, supportive care, treatment interruption and/or dose reduction. No patient discontinued rucaparib treatment due to a treatment-related AE. 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 I 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. The data suggest no relationship between QTcF increase and dose or exposure. In addition, there were no AEs suggestive of cardiac arrhythmia (eg, presyncope, syncope, sudden death) in any patient. ECG and AE data as of the cutoff date in patients receiving monotherapy rucaparib at doses up to 840 mg BID suggest there is a minimal risk of QTc prolongation.

In the Phase 1 portion, 2 patients (1 breast cancer, 1 ovarian cancer, both $gBRCA^{mut}$) achieved a RECIST CR and 7 patients (2 ovarian cancer, 4 breast cancer, 1 pancreatic cancer; all $gBRCA^{mut}$) achieved a RECIST PR (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). 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 wks at doses ≥360 mg BID in evaluable ovarian cancer patients is 92% (11/12). Responses have been durable across tumor types.

Preliminary efficacy data are available for 16 patients in the Phase 2 portion of Study CO-338-010. Currently, 12 of 16 (75%) patients have achieved a RECIST PR. Response to treatment occurs rapidly; the majority of these patients achieved a PR by the first disease assessment (week 6). All responses are ongoing, with several patients in Cycle 5 of treatment or beyond. The vast majority of patients had some level of target lesion measurement reduction as shown in Figure 1.

Figure 1 Best Response in Target Lesions – Phase 2 Portion of Study CO-338-010



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=14) at ≥240 mg BID with low inter-patient variability (<4-fold) within each dose group. Steady state trough levels also exhibited low intra-patient variability (24% coefficient of variation). 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.

Updates of study information may be found in the Investigator's Brochure.

3.3.2.1.2 Study CO-338-017

Study CO-338-017 (ARIEL2) is a Phase 2 study of rucaparib as monotherapy treatment for relapsed, platinum-sensitive high-grade ovarian, fallopian tube or primary peritoneal cancer. The purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer

patients for treatment with rucaparib. The trial is enrolling patients with and without a BRCA1/2 mutation in order to enable identification of this response signature, which will then be prospectively applied to the primary analysis of study CO -338-014 (ARIEL3). Tumor HRD status is assessed using next generation sequencing, with an algorithm for HRD status based on the presence of a BRCA mutation (germline or somatic) and/or degree of tumor genomic LOH, a phenotypic consequence of HRD.

All patients enrolled into Clinical Study CO-338-017 (ARIEL2) must have received at least 1 prior platinum-based treatment regimen, received a platinum-based regimen as their last course of treatment and have platinum-sensitive disease, defined as disease progression >6 months after the last dose of platinum. In addition, all patients must have disease that can be biopsied and is measurable by RECIST v1.1. Rucaparib 600 mg BID is administered continuously until disease progression.

Clinical Study CO-338-017 (ARIEL2) was initiated in October 2013. As of 27 June 2014, 72 of 180 planned patients have been enrolled. The median age is 65.5 years (range 44 – 83) and the majority of patients (n= 54, 75%) had Eastern Cooperative Oncology Group (ECOG) performance status of 0.

The most frequent (reported in ≥15% of patients treatment-related AEs (all grades) as of 27 June 2014 are gastrointestinal-related toxicities (nausea, constipation, vomiting, diarrhea, and abdominal pain), fatigue, elevations in ALT/AST, decreased appetite, and dysgeusia. Transaminase elevations occur early in treatment and are generally transient and resolve or stabilize. All patients who experienced AEs related to rucaparib, including those with Grade 3 transaminase elevation, were successfully managed by treatment interruption and/or a dose reduction. No patient has discontinued rucaparib due to a treatment-related AE. No patients have died on study or within 30 days of last dose of rucaparib.

Response data are preliminary, yet indicate that rucaparib has activity in $BRCA^{wt}$ patients with high level of LOH as well as in $BRCA^{mut}$ patients.

Updates of study information may be found in the Investigator's Brochure.

3.3.2.1.3 Study A4991002, A4991005, and A4991014

Further details of these studies are provided in the Investigator's Brochure.

3.3.2.1.4 Safety: Events of Special Interest

The current list of adverse events of special interest (AESIs) is located in the rucaparib IB.

3.4 Rationale for Study

In vitro studies have shown that cells deficient in BRCA1/2 as well as cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity in vitro.[18, 19, 27-30] Clinical data have shown that ovarian cancer patients with and without evidence of a gBRCA mutation benefit from treatment with a PARP inhibitor[20-24] and that maintenance treatment with a PARP inhibitor following a response to

platinum-based treatment increases PFS in patients with ovarian cancer.[31, 32] While patients with a BRCA mutation derived the most benefit, patients without evidence of a BRCA mutation also derived significant benefit.[23, 32] The purpose of this study is to evaluate PFS of patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy in order to identify the patients most likely to benefit from treatment with rucaparib. It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD associated with a BRCA gene mutation or other HR gene alteration.

Patients will be stratified into one of 3 HRD subgroups (tBRCA, nbHRD, and biomarker negative) (Appendix A) by Foundation Medicine's ICTA, which will determine HRD status through analysis of homologous recombination gene mutations in tumor tissue. Tumor DNA will also be assessed to detect the presence of genomic scars.[35-38] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). Homologous recombination gene mutation analysis and genomic scarring will also be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 trial. The Final Clinical Trial Assay (FCTA) analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the analysis of this Phase 3 study.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

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

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
1. To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups	1. Disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause (invPFS), in molecularly defined subgroups
Secondary Objectives	**Secondary Endpoints**
1. To evaluate patient-reported outcome (PRO) of disease related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18)	1. Time to a 4-point decrease in the DSR–P subscale of the FOSI-18
2. To evaluate PRO utilizing the complete FOSI-18	2. Time to an 8-point decrease in the total score of the FOSI-18
3. To evaluate survival benefit	3. Overall survival (OS)
4. To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups	4. Disease progression according to RECIST v1.1, as assessed by IRR, or death from any cause (irrPFS), in molecularly defined subgroups
5. To evaluate safety	5. Incidence of AEs, clinical laboratory abnormalities, and dose modifications
6. To determine the population PK of rucaparib	6. Individual model parameter estimates of rucaparib and covariates identification
Exploratory Objectives	**Exploratory Endpoints**
1. To evaluate the relationship between CA-125 levels and invPFS	1. Association between the change from baseline in CA-125 measurements and invPFS
2. To evaluate PFS2 (PFS on the subsequent line of treatment)	2. Time to the next event of disease progression or death, as assessed by the investigator
3. To evaluate ORR	3. ORR per RECIST v1.1, as assessed by both investigator and IRR, in patients with measureable disease at study entry

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints

4. To evaluate duration of response (DOR)	4. DOR per RECIST v1.1, as assessed by both investigator and IRR
5. To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)	5. PRO as measured by the total score on the EQ-5D
6. To explore the relationship between rucaparib exposure, efficacy, and safety	6. Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

5.1.1 Screening Phase

All patients will undergo screening assessments within 120 days prior to randomization.

The study will enroll patients with platinum-sensitive (defined as disease with confirmed radiologic relapse > 6 months after the last dose of the penultimate platinum regimen received), high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a response to platinum-based chemotherapy administered for relapsed disease. Patients must have received ≥ 2 prior platinum-based treatment regimens, inclusive of the regimen that must have been administered immediately prior to maintenance therapy in this trial. There is no limit on the number of prior platinum-regimens that may have been received, but the patient must have been sensitive to the penultimate platinum regimen received. In addition, up to 1 prior non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will not be counted as a non-platinum regimen. Prior maintenance therapy may have been administered with any prior treatment, with the exception of the platinum regimen received immediately prior to maintenance in this study. For the last chemotherapy course prior to study entry, patients must have received a platinum-based doublet chemotherapy regimen (minimum 4 cycles) and have achieved a CR (defined as complete radiologic response by RECIST [Appendix B] or PR (defined as partial response by RECIST [Appendix B] and/or a GCIG CA-125 response [Appendix C]. All responses require that CA-125 be < ULN. The response must be maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study.

Screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12 lead electrocardiogram (ECG), ECOG performance status, central laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of child-bearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, AEs, and radiologic assessment by CT or MRI. PRO will be collected using the FOSI-18 and EQ-5D instruments.

Germline BRCA mutation results should be obtained for all patients who are known to have been tested prior to enrollment in order to determine whether any mutation was reported and if so, whether the mutation was classified as deleterious/pathogenic or other. Enrollment of patients with a gBRCA mutation classified as deleterious (i.e. pathogenic), suspected deleterious, or the equivalent, on the most recent assessment by a testing laboratory will be limited to 150. Patients with a BRCA mutation detected in tumor tissue (tBRCA) will be limited to 200. Once this cap is

reached, newly screened patients identified as having a BRCA mutation in tumor tissue will be offered treatment in another study.

The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Results for the BRCA genes will be provided to patients who consent to receive this information upon availability. Results for the remainder of the gene panel will be provided to consenting patients upon treatment discontinuation. All results are to be disclosed to consenting patients by the study physician as part of an overall clinical discussion. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline BRCA testing, this result will be entered into the clinical trial database. The sponsor will remain blinded to all NGS test results (including all tBRCA results), as well as existing BRCA data, until the primary efficacy analysis is conducted.

Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. This data will be generated in a research setting and will not be provided to the investigator or patient. However, if an actionable mutation, as defined by the American College of Medical Genetics and Genomics, is revealed that was not classified as deleterious on the tumor-based NGS test report, these blood-based incidental findings will be made available to the investigator, provided the results are generated from a Clinical Laboratory Improvement Amendment-certified laboratory.[53]

Enrollment will require Clovis (or designee) review of eligibility, including, but not limited to:

- The number of prior therapies and the details for the penultimate and most recent platinum-based regimens, including dates administered;
- documentation supporting platinum sensitivity;
- documentation supporting a RECIST or GCIG CA-125 response to most recent platinum-based treatment;
- confirmation if patient has had local gBRCA testing;
- confirmation that sufficient tumor tissue was submitted for HRD stratification for randomization and storage for potential bridging to a validated companion diagnostic test and analysis results were successfully transmitted to IXRS

5.1.2 Randomization

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy, and is described in more detail in Section 7.2. Study treatment must be initiated within 3 days of randomization.

5.1.3 Double-Blind Treatment Phase

For patients remaining on treatment as of implementation of Protocol Amendment 5, a more limited number of assessments will be performed during the treatment period as compared to previously; however, an appropriate level of safety monitoring will remain in place. A revised Schedule of Assessments, which replaces all prior schedules of assessments and should be followed for all patients who remain on treatment or in long-term follow-up, is provided in Section 9.1.

During the double-blind treatment phase (continuous 28-day treatment cycles), patients will be monitored for safety and efficacy. Assessments will include AEs; serum pregnancy for women of child-bearing potential; complete blood count (monthly assessment advised); subsequent medications, therapies and procedures; and study drug administration and accountability. In addition, clinical chemistry, urinalysis, and vital signs may be performed per local standard of care practices.

Patients will be assessed for disease status per RECIST v1.1 every 12 calendar weeks (up to 1 week prior is permitted) following initiation of study treatment on Day 1 of Cycle 1. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter follow-up. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the protocol schedule of assessments. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

Sites were previously notified that as of 06 December 2019, CT scans (and other imaging, as appropriate) performed during the treatment period and at treatment discontinuation will no longer be collected for IRR.

Patients were continuously monitored for safety. An Independent Data Monitoring Committee (IDMC) with multidisciplinary representation evaluated safety in compliance with a prospective charter.

The IDMC was discontinued when the primary study endpoint of progression-free survival was reached.

5.1.4 Treatment Discontinuation

Upon treatment discontinuation, regardless of reason, patients will have a Treatment Discontinuation visit. Assessments at this visit will include AEs, serum pregnancy for women of child-bearing potential, disease status assessment, and study drug accountability; in addition, complete blood count, clinical chemistry, urinalysis, and vital signs may be performed per local standard of care practices. An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent prior to the start of any subsequent anticancer treatment. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy. All patients discontinued from treatment will be followed for 28 days following the last dose of study drug for the collection of AEs.

5.1.5 Follow-Up Phase

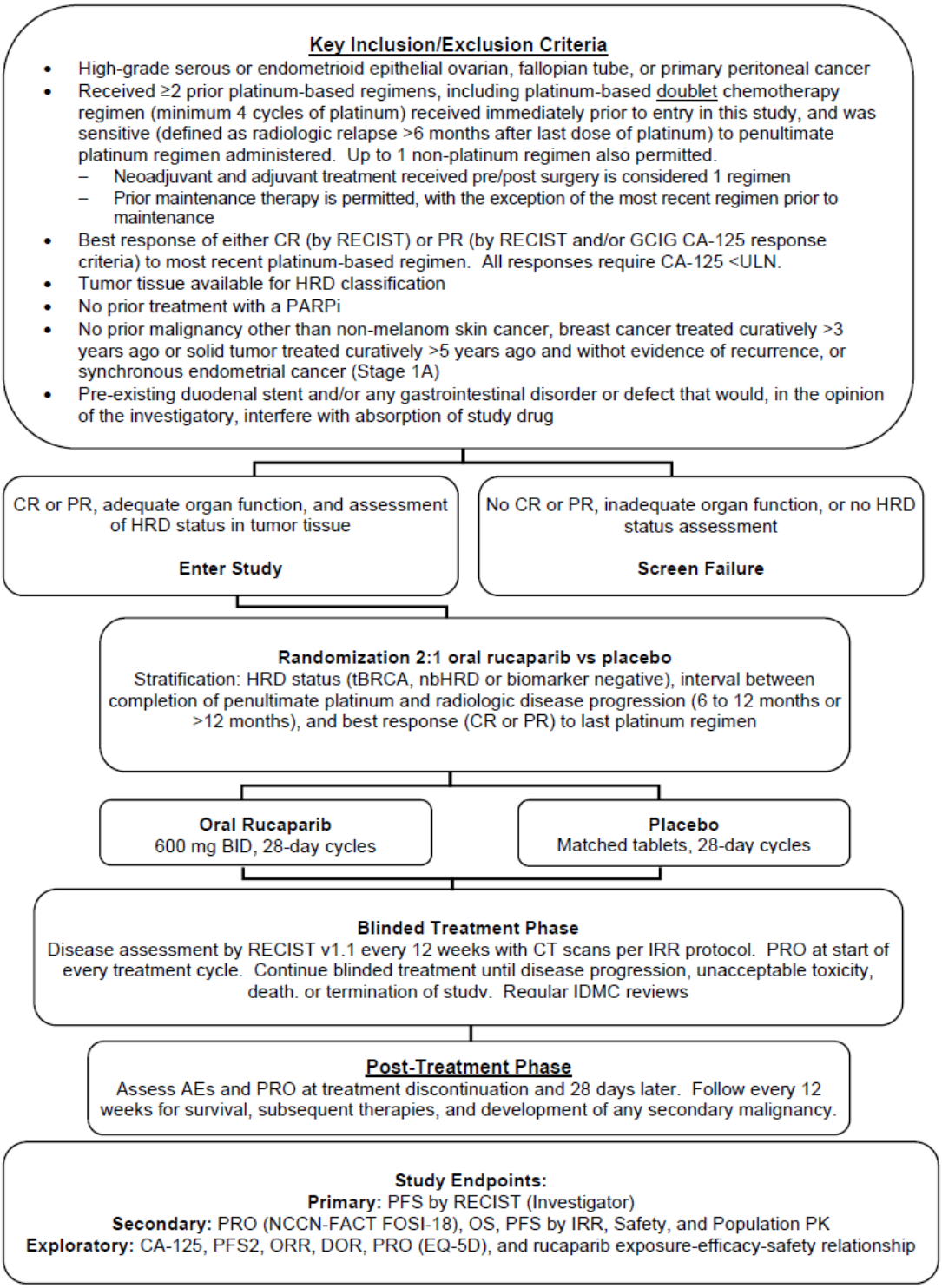
After the Treatment Discontinuation visit, all patients will be followed for AEs up to 28 days after last dose of study drug. All serious adverse events (SAEs) and AESIs are to be followed to resolution, stabilization, or lost to follow-up (refer to Section 10.7) even if the duration extends beyond the 28-day follow-up period. Patients will also be followed for survival, subsequent treatments, and monitoring for secondary malignancy approximately every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12 week intervals from Cycle 1 Day 1 (a window of up to 7 days prior is permitted) until disease progression by RECIST v1.1, as assessed by the investigator, or death. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

5.2 Study Schema

An overview of the study design is provided in Figure 2.

Figure 2 Study Schema



NOTE: With the implementation of Protocol Amendment 4, the collection of PRO data was no longer required. Other assessments have been revised with the implementation of Protocol Amendment 5. Please refer to the schedule of assessments (Table 3).

5.3 End of Study

The trial is monitored on an ongoing basis by an IDMC for the number of PFS events required for the primary endpoint and for safety signals. An unblinding of treatment assignment might be performed when the study is still ongoing if the IDMC recommends it. However, the study is not anticipated to close until all patients are off treatment and sufficient OS follow up has occurred, which could include patients being transferred to another study for OS follow up. Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of receiving rucaparib via another access mechanism.

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

5.4 Discussion of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study.

Sponsor personnel (with the exception of individuals responsible for clinical supply chain), investigator and clinical site staff, and patient will all be blinded to study treatment to avoid bias in the interpretation of the efficacy and safety results. To avoid bias between treatment groups, patients will be randomized to treatment with active drug or placebo with stratification according to HRD classification, interval between completion of penultimate platinum-based regimen and disease progression by radiologic assessment, and best response to platinum regimen received immediately before initiation of maintenance therapy.

PFS by RECIST will be assessed by the investigator for the primary endpoint (invPFS) and by a blinded independent radiologist for the secondary endpoint (irrPFS).

Ongoing benefit/risk will be assessed regularly by an IDMC that will have access to unblinded datasets. The IDMC will hold meetings and continue to review data until the protocol specified primary endpoint collection is complete (i.e., 70% of the patients in the tBRCA subgroup have an event of PFS) and the IDMC recommend the sponsor to unblind the treatment assignments for assessment of primary efficacy. The treatment assignment was unblinded in June 2017 for the primary efficacy analysis and thus no further IDMC meetings are planned. Unless a patient is unblinded for safety reasons or following approval by Clovis Oncology, all study investigators will remain blinded to patient treatment assignment until final study analysis.

6 STUDY POPULATION

6.1 Number of Patients and Sites

Approximately 540 patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer will be enrolled at approximately 90 – 100 study sites. A minimum of 180 and a maximum of 200 patients with a deleterious tBRCA mutation will be enrolled. Enrollment of patients with a known deleterious gBRCA mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.

6.2 Inclusion Criteria

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

1. Have signed 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 a histologically confirmed diagnosis of high-grade (Grade 2 or 3) 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
   - Grade 2 tumors classified under a 3-tier system should be re-reviewed by local pathology and confirmed as high-grade under the 2-tier system
4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e. documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered)
   - Received ≥2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will <u>not</u> be counted as a non-platinum regimen.
   - There is no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered.
   - If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen
   - Prior maintenance therapy following a prior treatment regimen is permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anticancer therapy is permitted to be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial.

5. Achieved best response of either CR or PR to the most recent platinum-based regimen administered and is randomized to study treatment within 8 weeks of the last dose of platinum received
   - The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the 2nd chemotherapy agent is per investigator' discretion.
   - A minimum of 4 cycles of platinum chemotherapy must have been administered. There is no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of therapy for the specific purpose of enabling patient eligibility and randomization within 8 weeks of the last platinum dose is not permitted.
   - A CR is defined as a complete radiologic response per RECIST v1.1, i.e. absence of any detectable disease and CA-125 <ULN*
   - A PR is defined as either a partial response per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serologic response per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1)*
     - CA-125 must also be <ULN for all responses classified as a PR
   - R0 surgery (no visible tumor) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen is not permitted. The response assessment must be determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 >2 x ULN immediately prior to the chemotherapy regimen is required.
   - Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study
   - All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record
6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 – 12 x 10 µm sections, or equivalent) available for planned analyses.
   - The most recently collected tumor tissue sample should be provided, if available
   - Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample
   - Sample must be received at the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization
7. Have CA-125 measurement that is < ULN
8. Have ECOG performance status of 0 to 1
9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug:
   - Bone Marrow Function
     - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

- Platelets > 100×10^9/L
- Hemoglobin ≥ 9 g/dL

– Hepatic Function

- Aspartate aminotransferase (AST) and ALT ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
- Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)

– Renal Function

- Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula

* Note: It is acceptable for sites to utilize local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it is not a requirement to re-read radiological scans to collect this data.

6.3 Exclusion Criteria

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

1. History of a prior malignancy except:
   – Curatively treated non-melanoma skin cancer
   – Breast cancer treated curatively >3 years ago, or other solid tumor treated curatively >5 years ago, without evidence of recurrence
   – Synchronous endometrioid endometrial cancer (Stage 1A G1/G2)
2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible.
3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study
4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study drug
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
7. Pregnant or breast feeding. Women of child-bearing potential must have a negative serum pregnancy test ≤ 3 days prior to first dose of study drug
8. 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 study drug and/or ongoing adverse effects from such treatment > NCI-CTCAE Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug

  - Ongoing hormonal treatment for previously treated breast cancer is permitted
  - Refer also to inclusion criteria #4 for guidelines pertaining to prior maintenance therapy

9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F)
10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study

6.4 Patients or Partners of Patients of Reproductive Potential

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

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

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

Female patients of child-bearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of study drug. In addition, a serum pregnancy test must be performed within ≤ 3 days prior to Day 1 of every subsequent cycle during the treatment phase and at the Treatment Discontinuation visit. All pregnancy testing will be performed by the local laboratory.

Female patients of reproductive potential must practice highly effective methods of contraception (failure rate < 1% per year) with their male partners during treatment and for 6 months following the last dose of study drug. Highly effective contraception includes:

- Ongoing use of progesterone-only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon);
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);

- Bilateral tubal occlusion;
- 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 (eg, calendar, symptothermal, post-ovulation methods) is not acceptable.

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

6.5 Waivers of Inclusion/Exclusion Criteria

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

7 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 and matched placebo tablets will be supplied to the study sites by the sponsor. A brief description of the investigational product is provided below.

Drug Name:	CO-338
rINN:	rucaparib
Formulation:	Tablet; film coated; 120 mg (salmon, oval), 200 mg (blue, round, debossed with C2), 250 mg (white, rounded diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3)
How Supplied:	120, 200, 250, and 300 mg (as free base) strength tablets in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive one or more strengths.
Storage Conditions:	15–30 °C/ 59-86 ºF

Placebo tablets will be identical in appearance to the rucaparib tablets, matched for each strength.

Study drug containers containing rucaparib or placebo tablets will be labeled according to national regulations for investigational products together with the batch expiry date. Exceptionally, where accepted, the expiry date for the 120 mg strength tablets will not appear on the labels, but will be controlled by the use of an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

7.2 Method of Assigning Patients to Treatment Groups

Following confirmation of eligibility in the screening phase, patients will be randomized 2:1 to receive rucaparib or placebo. Randomization will occur by a central randomization procedure using IVRS/IWRS. The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced:

- HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A)
- Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment
- Best response (CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response] to platinum regimen received immediately prior to initiation of maintenance therapy. All responses require that CA-125 be <ULN.

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study treatment must be initiated within 3 days of randomization.

7.3 Preparation and Administration of Protocol-Specified Treatment

The investigator or designee will be responsible for distributing study drug to all patients. Study drug will be assigned by the IVRS/IWRS according to the patient's randomization assignment. The system must be accessed at each dispensation in order to retrieve the bottle number appropriate to the patient's treatment. Study sites should follow local guidelines for the handling of oral cytotoxic drugs.

All patients will ingest study drug twice a day. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Each dose should be taken with at least 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole.

Patients should take study drug doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (i.e. does not take it within 4 hours of the scheduled time), she should skip the missed dose and resume taking study drug with their next scheduled dose. Missed or vomited doses should 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 bring their study drug tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel. A compliance check and tablet count will be performed by study personnel during clinic visits and the dose dispensation will be entered in the eCRF.

- Once available supplies of 120 mg tablets/matching placebo are exhausted or the expiry date is reached, patients receiving this dose strength will be transitioned to 200 mg, 250 mg or 300 mg tablets/matching placebo, or combination of dose strengths. If/when patients are transitioned from 120 mg to 200 mg, 250 mg, or 300 mg strength tablets, the investigator has the discretion to select the dose most appropriate for the patient, rounding up or down as necessary.

- The dose that a patient will receive upon transition from 120 mg to 200 mg, 250 mg or 300 mg tablets/matching placebo will be agreed upon between the investigator and sponsor (or designee) in advance of any dosing change.

7.3.1 Dietary Restrictions

All patients participating in the study should be instructed not to consume any grapefruit products or any of the CYP1A2 or CYP3A4 inhibitors noted in Appendix F for 7 days prior to their first scheduled dose of oral rucaparib or placebo.

7.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

7.4.1 Starting Dose

The starting dose in this study will be 600 mg rucaparib or matched placebo, BID.

7.4.2 Dose Modification Criteria

Treatment with study drug should be held if any of the following are observed and a dose reduction should be considered or implemented:

- Grade 3 or 4 hematologic toxicity

  Grade 3 or 4 non-hematologic toxicity (except for 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 study drug may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

MANAGEMENT OF STUDY DRUG TREATMENT-EMERGENT ALT/AST ELEVATIONS

- Grade 4 ALT/AST elevations: hold study drug until values have returned to Grade 2 or better, then resume study drug with a dose reduction. Monitor liver function tests weekly for 3 weeks after study drug 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 study drug 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 study drug, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before study drug can be resumed, either at the current dose or at a reduced dose.

Treatment with study drug should be held until the toxicity resolves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event to ≤ CTCAE Grade 2. If a patient continues to experience toxicity despite dose reduction to 240 mg/300 mg BID rucaparib or placebo, or if dosing with study drug is interrupted for > 14 consecutive days due to toxicity, treatment discontinuation or further dose reduction should be discussed and agreed between the investigator and the sponsor.

MANAGEMENT OF NEW OR WORSENING PULMONARY SYMPTOMS

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high-resolution CT scan) in consultation with a

pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with study drug may be interrupted or continued per investigator discretion. If study drug is given in combination with another agent, the contribution of the other agent should also be assessed independently.

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

Refer to Section 10.3 and Section 10.8 of the protocol for additional information regarding classification and reporting of pneumonitis (and related events) as an AESI.

Dose reduction steps are presented in Table 2.

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

Table 2. Dose Reduction Steps

Tablets	**120 mg**	**200/250/300 mg**
Starting Dose	**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
*Additional dose reduction steps should be discussed with the medical monitor.		

7.4.3 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥75 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation. An IVRS/IWRS will be used to manage study drug inventory at all sites. In order to function properly, and to ensure patients receive the correct study drug according to the treatment assigned at randomization, the system will require real-time entry of study drug receipt, dispensation, or destruction, etc. by study personnel at the study center.

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

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

7.6 Blinding/Masking of Treatment

Active and matching placebo tablets of the same dose strength will be identical in appearance and supplied in identical containers. The medication labeling will ensure that no staff member or patient will be able to identify whether the tablets are placebo or contain active medication.

Patients will take the equivalent number of active or placebo tablets according to the treatment assignment and scheduled dose.

In the event of a medical emergency, an individual patient's treatment assignment may be unblinded using IVRS/IWRS. The module to unblind treatment assignment is accessible only to specific authorized study personnel. AEs per se are not a reason to break the treatment code. Unblinding should only occur for medical emergencies that require explicit knowledge of the treatment administered in order to determine the next course of action. The IVRS/IWRS vendor operates a 24-hour/365-day helpline as a back-up in the rare event the electronic system is unavailable when unblinding is required.

The study will not be unblinded for overall safety evaluation.

7.7 Treatment Compliance

Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose as well as requirements to return all containers at next clinic visits for accountability purposes. A compliance check and tablet count will be performed by study personnel during clinic visits and the dose dispensation will be entered in the eCRF.

8 PRIOR AND CONCOMITANT THERAPIES

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

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

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

8.1 Anticancer or Experimental Therapy

No anticancer therapy is permitted to have been administered as maintenance treatment in the interval period between completion of the most recent platinum-based chemotherapy and initiation of maintenance treatment in this study.

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study, with the exception of ongoing hormonal treatment for previously treated breast cancer.

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

8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP-interaction clinical study CO-338-044, rucaparib is a moderate inhibitor of CYP1A2, a weak inhibitor of CYP2C9, CYP2C19, and CYP3A, and shows no clinically significant effect on P-gp. Caution should be used in patients taking concomitant medicines that are substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A with narrow therapeutic windows; dose adjustments may be considered, if clinically indicated (Appendix F). Please refer to current IB for further information.

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

8.4 Bisphosphonates

Bisphosphonates are permitted.

8.5 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be exercised in patients receiving study drug and concomitant warfarin (Coumadin). Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard institutional practice.

8.6 Other Concomitant Medications

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

Rucaparib marginally increased digoxin area under the plasma concentration-time curve (AUC) by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

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

8.7 General Restrictions

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

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 3 **summarizes the procedures and assessments to be performed for all patients remaining on treatment or in follow up as of implementation of Protocol Amendment 5. The revised evaluations should commence immediately after the patient has provided appropriate informed consent, maintaining previous treatment cycle and day sequence.**

The revised Schedule of Assessments replaces all prior schedules of assessment.

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

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

Table 3. Schedule of Assessments After Implementation of Amendment 5

Procedure[a]	Blinded Treatment Phase (±3 days) Cycle X Day 1	Post-Treatment Phase		
		Treatment Discontinuation	28-day Follow-up	Long-term Follow-up
Adverse Events[b]	The investigator should monitor and educate patients on possible AEs observed with rucaparib		X	
Complete Blood Count	Monthly assessments advised			
Clinical Chemistry, Urinalysis, Vital Signs	Local standard of care practices per investigator			
Serum Pregnancy Test (WOCBP only)[c]	X	X		
Disease Assessment (Tumor Scans/CA-125)[d]	X[e]	X	X[f]	X[f]
Study Drug Dispensation/Administration/Accountability	X	X		
Tumor Tissue Biopsy (optional)[g]		X		
Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[h]			X	X

Abbreviations: AE = Adverse event; AESI = adverse event of special interest; CA-125 = cancer antigen 125; CR = complete response; CT = computed tomography; GCIG = Gynecologic Cancer InterGroup;MRI = magnetic resonance imaging; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of child-bearing potential.

[a] The study visit window in the double-blind treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the subject's investigational product supply. Study drug should be dispensed as applicable.

[b] AEs will be monitored but only SAEs/AESIs are recorded through 28 days after last dose of rucaparib. Only treatment-related SAEs and all AESIs, regardless of causality, need to be reported after the 28-day window. Ongoing SAEs and AESIs will be followed until resolution, stabilization, or lost to follow-up.

[c] Women of child-bearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of study drug. A serum pregnancy test must also be performed ≤ 3 days prior to Day 1 of every cycle during the treatment phase and at the treatment discontinuation visit. All tests will be performed by a local laboratory.

[d] Disease 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 assessment techniques (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. CT/MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline.

[e] Tumor scans to be performed every 12 calendar weeks (a 7-day window prior is permitted) after start of treatment on Day 1 of Cycle 1. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new

lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

[f] To be performed every 12 calendar weeks (up to 7 days prior is permitted) through to investigator-assessed radiologic disease progression by RECIST v1.1 for any patient who discontinued from study treatment for reason other than disease progression or death. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

[g] An optional tumor biopsy may be collected from patients from time of radiographic disease progression until the start of the subsequent anticancer treatment. Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy.

[h] All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments, secondary malignancy, and survival approximately every 12 weeks (± 14 days) from Cycle 1 Day 1 until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports) and should be reported as specified in Section 10.

9.2 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to randomization. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

Up to 120 days prior to randomization:

- Medical history, including demographic information (birth date, race, gender, etc.) and smoking status, and oncology history, including date of diagnosis for ovarian, primary peritoneal, or FTC (and other malignancy, if applicable), prior treatments received, dates of administration, best response achieved, date of progression and how assessed, radiology reports, and gBRCA mutation status (if known)
- FFPE archival tumor tissue sample. Sufficient archival FFPE tumor tissue (enough for 1 x 4 µm section for H&E and approximately 8 to 12 x 10 µm sections, or equivalent) for planned analyses should be provided. Refer to the Pathology Charter for detailed sample handling instructions.
    - The most recently collected tumor tissue sample should be provided, if available.
    - Submission of a tumor block preferred; if sections are provided, these must all be from the same tumor sample.
    - Tumor content ≥30% is strongly preferred for successful genomic scarring/LOH analysis
    - Sample must be submitted to the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization
- AE monitoring (only if related to screening procedure)

Up to 28 days prior to randomization:

- PRO collected using the FOSI-18 and EQ-5D instruments
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG
- Prior and concomitant medications and any surgical procedures
- Disease assessment/tumor scans: tumor assessments should consist of clinical examination and appropriate imaging techniques (including 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. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment. CT/MRI scans of the chest, abdomen, and pelvis

performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline.

- ECOG performance status (Appendix D)
- AE monitoring (only if related to screening procedure)

Up to 14 days prior to randomization:

- Hematology (RBC and parameters [Hgb, Hct, MCH, MCV, and MCHC] and reticulocyte count, white blood cell [WBC] and differential [with ANC], and platelet count
- Serum chemistry (total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, blood urea nitrogen [BUN] or urea, total bilirubin, alkaline phosphatase (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). *Note: fasting is not required.*
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones) ≤14 days prior to the first dose of study drug. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings
    - CA-125 measurement
- AE monitoring (only if related to screening procedure)

Up to 3 days prior to first dose of study drug:

- Serum pregnancy test for women of child-bearing potential
- AE monitoring (only if related to screening procedure)

9.3 Treatment Phase

9.3.1 Day 1 of Cycles 1 and 2

The following procedures/assessments will be completed before study drug is administered:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital Signs
- Concomitant medications and procedures
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry (fasting is not required)

- Serum pregnancy for women of child-bearing potential (Cycle 2 only)
- CA-125 measurement (Cycle 1 only)
- Blood sample for storage (Cycle 1 only; if sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter)
- Study drug dispensation
- AE monitoring
- Plasma PK sample (prior to first dose taken that day) (Cycle 2 only; see Section 9.5.1)
- Serum sample for alpha-1 acid glycoprotein (AAG) sample (Cycle 2 only)

Study drug will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest study drug twice daily at about the same times every day, as close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

Patients will be instructed to refrain from taking their first dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

9.3.2 Day 15 of Cycles 1 and 2

The following procedures will be completed:

- Concomitant medications and procedures
- Hematology
- Serum chemistry (fasting is not required)
- AE monitoring
- Plasma PK sample (in morning or afternoon following the first dose of study drug taken this day; see Section 9.5.1)
- Serum sample for AAG analysis *(note: sample can be collected at the same time as hematology and serum chemistry and/or with the PK sample)*

Patients will ingest study drug twice daily at about the same times every day, at close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

9.3.3 Cycles 3 and Beyond

The revised Schedule of Assessments shown in Table 3 replaces all prior schedules of assessments as of implementation of Protocol Amendment 5.

Disease assessment/tumor scans will be performed every 12 calendar weeks (within 7 days prior is permitted) after start of treatment on Day 1 of Cycle 1. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

The following procedures are advised:

- Hematology (complete blood count); monthly assessments advised
- Clinical chemistry, urinalysis, and vital signs according to local standard of care per investigator
- Serum pregnancy for women of child-bearing potential
- CA-125 measurement (Day 1 of Cycles 4, 7, 10, etc.)
- AE monitoring
- Study drug accountability

Study drug will be dispensed to the patient in sufficient quantity to last until the next clinic visit. A single dose of study drug will be administered during the current clinic visit with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal).

Patients will continue dosing with study drug at home on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal), taking doses twice daily at about the same times every day. Study drug should be taken with at least 8 oz (240 mL) of room temperature water.

9.4 Post-Treatment Phase

9.4.1 Treatment Discontinuation

The revised Schedule of Assessments shown in Table 3 replaces all prior schedules of assessments as of implementation of Protocol Amendment 5.

Upon treatment discontinuation, regardless of the reason, patients will have a Treatment Discontinuation visit. The following procedures will be performed:

- Tumor scans (using the same methodology as was used at screening) if reason for treatment discontinuation was other than disease progression based on radiologic assessment
- CA-125 measurement
- Study drug accountability

The following procedures are advised:

- ECOG performance status (Appendix D)

- Hematology (complete blood count)
- Clinical chemistry, urinalysis, and vital signs according to local standard of care per investigator
- Serum chemistry (fasting is not required)
- Serum pregnancy test for women of child-bearing potential
- AE monitoring
- Optional tumor tissue biopsy collection at time of disease progression/treatment discontinuation until the start of the subsequent anticancer treatment (requires additional consent). If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy. Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

9.4.2 28-day Follow-up

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

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.
- AE monitoring (only SAEs/AESIs are recorded through 28 days after last dose of rucaparib. Ongoing SAEs and AESIs will be followed until resolution, stabilization, or lost to follow-up).
- Subsequent treatments, secondary malignancy monitoring, and overall survival (OS)

9.4.3 Long-term Follow-up

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.
- Subsequent treatments, secondary malignancy monitoring, and OS information will be collected for all patients approximately every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports) and should be reported as indicated in Section 10.8.

- SAEs related to study drug and all AESIs, irrespective of causality, are to be reported as specified in Section 10.8.

9.5 Methods of Data Collection

Hematology, clinical chemistry, urinalysis, serum CA-125, and serum pregnancy in women of child-bearing potential will be performed locally.

9.5.1 Pharmacokinetic Evaluations and AAG Measurement

As of implementation of Protocol Amendment 5, samples will no longer be collected for PK and AAG analyses.

9.5.2 Biomarker Analysis – FFPE Tumor Tissue

Archival tumor tissue must be located during the screening process and submitted **to the central laboratory directly** as soon as possible for determination of HRD status. Archival tumor tissue is required for HRD stratification for randomization and for storage for potential bridging to a validated companion diagnostic test.

9.5.3 Biomarker Analysis – Blood

As of implementation of Protocol Amendment 5, blood samples will no longer be collected for biomarker analyses.

9.5.4 Safety Evaluations

9.5.4.1 Adverse Event Assessment

The investigator is responsible 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 after the first dose of study drug and until 28 days after the last dose of study drug. Any ongoing SAEs and AESIs will be recorded and followed until resolution, stabilization, or loss to follow-up. Only treatment-related SAEs and all AESIs, regardless of causality, need to be reported after the 28-day window. SAEs will be graded according to the NCI-CTCAE grading system (v4.03) and recorded on the eCRF.

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

9.5.4.2 Prior and concomitant medications

Prior concomitant medications will be recorded during screening and concomitant medications will be collected from study entry until the Treatment Discontinuation visit.

9.5.4.3 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: As of implementation of Protocol Amendment 5, monthly hematology assessment, consisting of a complete blood count, is advised.

Clinical Chemistry: As of implementation of Protocol Amendment 5, clinical chemistry assessments may be performed according to local standard of care per investigator.

Urinalysis: As of implementation of Protocol Amendment 5, urinalysis may be performed according to local standard of care per investigator.

Laboratory reports should be reviewed by the investigator or delegated physician who will assess clinical significance.

Serum Pregnancy: For women of child-bearing potential only. Serum pregnancy testing is to be performed ≤ 3 days prior to first dose of study drug, ≤ 3 days prior to the start of every cycle during the treatment phase, and at the Treatment Discontinuation visit.

9.5.4.4 Vital Signs

As of implementation of Protocol Amendment 5, vital signs may be performed according to local standard of care per investigator.

9.5.4.5 12-Lead Electrocardiograms

As of implementation of Protocol Amendment 5, ECGs will no longer be a required procedure for this protocol.

9.5.4.6 Body Weight and Height

As of implementation of Protocol Amendment 5, body height and weight assessments will no longer be a required procedure for this protocol.

9.5.4.7 Physical Examinations

As of implementation of Protocol Amendment 5, physical examinations will no longer be a required procedure for this protocol.

9.5.4.8 ECOG Performance Status

As of implementation of Protocol Amendment 5, ECOG performance status assessments will no longer be a required procedure for this protocol.

9.5.5 Efficacy Evaluations

9.5.5.1 Disease Assessments

Tumor assessment measurements will be performed at screening, at the end of every 12 weeks of treatment (up to 1 week prior permitted) relative to Cycle 1 Day 1, at discontinuation of treatment, and as clinically indicated. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

Disease assessment will comprise clinical examination and appropriate imaging techniques (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. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. Investigators should perform scans of other anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. Imaging guidelines provided in the Bioclinica Site Manual should be followed for the collection of images and the radiological assessment of disease.

Tumor response will be interpreted using RECIST v1.1 (Appendix B). Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator. Patients who have been on study at least 18 months may decrease the frequency of disease assessments to every 16 (±2) weeks. Investigator should consult with sponsor's medical monitor before decreasing frequency.

9.5.5.2 Tumor Markers

CA-125 measurement will be performed at screening, on Day 1 of Cycle 1, at the start of every 3rd cycle thereafter (i.e., Day 1 of Cycle 4, Cycle 7, Cycle 10, etc.), at discontinuation of treatment, and as clinically indicated.

9.5.6 Patient-Reported Outcomes

With the implementation of Protocol Amendment 4, the collection of patient-reported outcomes was no longer required.

9.5.7 Appropriateness of Measurements

The assessments planned in the protocol are widely used and recognized as reliable, accurate and relevant.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product. The pharmaceutical product does not necessarily have a causal relationship with the AE. 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 (eg, "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). 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.

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose that:

- Results in death.
- Is immediately life-threatening (i.e. the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or the development of drug dependency or drug abuse.

10.3 Definition of an Adverse Event of Special Interest

An AESI (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 (eg, 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 IB. These AESIs are to be reported to the sponsor expeditiously (see Section 10.8 for reporting instructions).

Report any AE of pneumonitis, or any of the following AEs, irrespective of causality assessment and severity, as an AESI within 24 hours using the study Serious Adverse Event Form and the applicable procedures as outlined in Section 10.8:

- pneumonitis
- interstitial lung disease
- pulmonary fibrosis
- acute interstitial pneumonitis
- alveolitis necrotizing
- alveolitis
- hypersensitivity pneumonitis
- organizing pneumonia

10.4 Exceptions to Serious Adverse Event Reporting

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 (eg, respite care).
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward).
- Overdose of either study drug or concomitant medication, unless associated with an SAE. If the event does not meet SAE criteria, it should still be captured as a non-serious AE on the appropriate eCRF.
- 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

It is the responsibility of the investigator to assess the clinical significance of all abnormal laboratory values as defined by the list of reference ranges from the local laboratory. In some

cases, significant change in laboratory values within the normal range may require similar assessment.

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

- It resulted in treatment modification (reduction of dose, interruption of dosing, or permanent discontinuation of study drug)
- It required intervention/management
- It is suggestive of organ toxicity
- The investigator considers it to be clinically significant

10.6 Pregnancy or Drug Exposure during Pregnancy

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

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

All pregnancies should be followed through to outcome whenever possible. Once the outcome of a pregnancy is known, the Clinical Pregnancy Outcome Report form should be completed and submitted to the sponsor.

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

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

As of the implementation of Amendment 5, only SAEs/AESIs will be fully documented on the appropriate eCRF. For each SAE/AESI, the investigator must provide duration (start and end dates or ongoing), intensity, relationship to study drug, and indicate whether specific action or therapy was required.

Any SAE/AESI that occurs after the first dose of study drug until 28 days after last dose of study drug administration will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed within this protocol, whether dosing has occurred or not. 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 on the AE eCRF and, if applicable, the SAE report form. Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that

constitute a single disease entity or syndrome into a final diagnosis. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

All SAEs/AESIs that occur during the study or within 28 days after receiving the last dose of study drug, regardless of relationship to study drug, must be reported to the sponsor/designated safety contact immediately (i.e., within 24 hours of the investigator's knowledge of the event). 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. 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. If a patient is determined to be a screen failure, no further AEs/SAEs are required to be reported once that determination has been made, with the exception of AEs/SAEs deemed related to a protocol-specified procedure. Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.7.4.

10.7.1 Intensity of Adverse Events

Severity refers to the intensity of an AE. The severity of each AE will be categorized using the NCI-CTCAE, v4.03.[54]

For any term that is not specifically listed in the CTCAE, intensity should be assigned a grade of 1-5 using the following CTCAE guidelines:

- Mild (Grade 1): mild or asymptomatic symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): limiting age-appropriate instrumental activities of daily living; minimal, local or noninvasive intervention indicated
- Severe (Grade 3): limiting self-care activities of daily living; hospitalization indicated
- Life threatening (Grade 4): life-threatening consequences; urgent intervention indicated
- Fatal (Grade 5): results in death

10.7.2 Causal Relationship of Adverse Events to Study Drug

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

Not Related To Study Drug	An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medication, disease under study, etc.) An AE that does not follow a reasonable temporal sequence from administration of the study drug. An AE that does not follow a known pattern of response to study drug. An AE that does not reappear or worsen when study drug is restarted. An AE for which an alternative explanation is likely, but not clearly identifiable.

Related to Study Drug	An AE that is difficult to assign to alternative causes. An AE that follows a strong or reasonable temporal sequence from administration of study drug. An AE that could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. An AE that follows a known response pattern to study drug. An AE that is confirmed with a positive rechallenge or supporting laboratory data.

10.7.3 Outcome

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

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Improved
- Ongoing
- Death
- Unknown/Lost to follow-up

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

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized until 28 days after the last dose of study treatment. Any SAE/AESI must be followed until the event has resolved, the condition has stabilized, or the patient is lost to follow up. If the patient is lost to follow-up with an ongoing SAE/AESI, this should be captured accordingly on a follow-up SAE/AESI report.

10.8 Regulatory Aspects of Adverse Event Reporting

All SAEs and AESIs, irrespective of relationship to study treatment, as well as all pregnancies, must be reported to the sponsor's SAE designee **within 24 hours** of knowledge of the event, occurring during the study through 28 days after receiving the last dose of study treatment, according to the procedures below. After the 28-day specified window, SAEs considered to be treatment related and all AESIs, regardless of treatment relationship, should be reported if occurring. Pregnancies that occur within 6 months of the last dose of study drug should be reported. It is important that the investigator provide an assessment of relationship of the SAE/AESI to study treatment at the time of the initial report. The SAE/AESI Report form must be used for reporting SAEs/AESIs. The contact information for reporting of SAEs/AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

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 the Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the

European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), 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.

10.9 Independent Data Monitoring Committee

No formal efficacy interim analyses are planned.

An IDMC will be established to review safety and efficacy data in compliance with a prospective charter and will be involved until the primary endpoint has been met and the study unblinded. The IDMC will be comprised of medical oncologists with experience in treating women with ovarian cancer and a statistician, all of whom are not otherwise involved in the study as investigators. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter, which will be endorsed and signed by the IDMC prior to the first data review meeting.

The IDMC will:

- Review safety and efficacy of rucaparib compared with placebo to ensure the study is beneficial to patients
- Ensure the study is conducted in a high quality manner
- Monitor the size of the tBRCA subgroup and the known gBRCA group

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup. The IDMC will meet at least semi-annually after sufficient data has been collected. The IDMC chairperson may convene formal IDMC meeting if there are safety concerns. The sponsor can also request an IDMC review of safety data.

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

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

Intent-to-treat (ITT) Population – The ITT population will consist of all randomized patients.

11.2 Statistical Methods

11.2.1 General Considerations

Variables registered on a continuous scale will be presented using the following descriptive statistics: N, mean, standard deviation, median, minimum and maximum. Continuous variables may also be presented using frequencies and percentages among appropriate categorizations. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The number of patients with events and the number of censored patients will also be presented. The stratified logrank test will be used to compare the time-to-event distributions between the randomized treatment groups. In addition, the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

The primary and key secondary endpoints will be tested among the tBRCA and all HRD subgroups, and all randomized patients, using an ordered step-down multiple comparisons procedure. Investigator determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant, then invPFS will be tested in the all HRD subgroup followed by invPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the FOSI-18 DRS-P subscale will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure.

PFS by IRR will be evaluated as a stand-alone secondary endpoint.

All data will be used to their maximum possible extent but without any imputations for missing data.

All statistical analyses will be conducted with the SAS® System, v9.1 or higher.

Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

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

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

The following variables will be summarized with frequency tabulations:

- Time since diagnosis (months): > 12-24, > 24
- Baseline laboratory parameters: graded based on CTCAE
- HRD status for stratification at randomization: tBRCA, nbHRD, biomarker negative
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months of >12 months) by radiologic assessment
- Best response to most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST v1.1 with normalization of CA-125] or PR [defined as partial radiologic response by RECIST v1.1 and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN.

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

11.2.4 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population.

11.2.4.1 Primary Efficacy Analysis

The primary efficacy endpoint for the study is invPFS by RECIST v1.1. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria (Appendix B), as assessed by the investigator, or death due to any cause, in molecularly defined subgroups. The stratification factors included in the primary analysis of invPFS will be as follows:

- HRD classification (tBRCA or nbHRD or biomarker negative)
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment
- Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST v1.1 with normalization of CA-125] or PR [defined as partial response by RECIST v1.1 and/or a GCIG CA-125 response]). All responses required that CA-125 be <ULN.

Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly-defined HRD subgroups) can be assessed prospectively.

11.2.4.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are:

- Time to a 4-point decrease in the FOSI-18 DSR–P subscale
- Time to an 8-point decrease in the FOSI-18 total score
- OS
- PFS by RECIST v1.1 as assessed by IRR (irrPFS)

PRO of disease-related symptoms as measured by the FOSI-18 DRS–P subscale

The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS-P subscale. Patients without a 4-point reduction will be censored on the date of their last PRO evaluation.

PRO as measured by the total score of the FOSI-18

An event in worsening of PRO utilizing the complete FOSI-18 instrument will be defined as the time from randomization to an 8-point reduction in the total score. Patients without an 8-point reduction will be censored on the date of their last PRO evaluation.

Overall survival

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive.

An interim OS was determined at the time of the primary endpoint unblinding (Section 11.3). The final OS analysis will be performed at the time of the study close. See Section 11.3 for further details.

irrPFS

PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first.

11.2.5 Safety Analyses

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

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

11.2.5.1 Adverse Events

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

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

Separate tables will be presented as follows:

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

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

11.2.5.2 Clinical Laboratory Evaluations

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

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

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

11.2.5.3 Vital Sign Measurements

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

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

11.2.6 Population PK Analysis

The PK endpoint is individual model parameter estimates of rucaparib and covariates identification.

A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.7 Exploratory Analyses

The endpoints for the exploratory analyses are:

- Change from baseline in CA-125 measurements by the central laboratory
- PFS2 (PFS on the subsequent line of treatment) defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- ORR per RECIST v1.1, as assessed by both the investigator and IRR, in patients with measureable disease at study entry
- DOR per RECIST v1.1, as assessed by both the investigator and IRR
- PRO as measured by the EQ-5D total score
- Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

11.2.7.1 Change from Baseline in CA-125

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the CA-125 measurements from the central laboratory. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

The association between the change from baseline in CA-125 measurements and invPFS will be evaluated using a Cox proportional hazards model. A measure of CA-125 kinetics such as the rate of change from baseline in CA-125 may also be associated with invPFS using a Cox model.

11.2.7.2 Progression Free Survival 2 (PFS2)

The second event of PFS, PFS2, is defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. The first event of disease progression will be captured as the primary endpoint in this study and thus the second event will be the next event of disease progression as assessed by the investigator. This second event of PFS may be a documented event per RECIST guidelines or may be an event of symptomatic progression.

11.2.7.3 Overall Response Rate

ORR is defined as a best response of CR or PR using the RECIST v1.1 criteria (Appendix B), as assessed by both investigator and IRR, in patients with measurable disease at study entry. ORR will be summarized with frequencies and percentages in the safety population.

11.2.7.4 Duration of Response

The DOR is measured from the time measurement criteria are met for CR/PR per RECIST v1.1 criteria (Appendix B), as assessed by both the investigator and IRR, until the first date that recurrent or progressive disease (PD) is objectively documented. The DOR will be summarized with descriptive statistics. Only patients with a response will be included in the summary.

11.2.7.5 Patient Reported Outcome EQ-5D

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

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

11.2.7.6 Relationship between Rucaparib Exposure and Efficacy and Safety

The primary endpoint of invPFS will be presented for subgroups of patients defined by levels of rucaparib exposure. These analyses are exploratory in nature so the definition of relevant subgroups may be data-driven.

11.3 Interim Analysis

No formal interim efficacy analyses will be performed.

All endpoints were summarized at the time the primary endpoint (invPFS) was unblinded in April 2017; however, the following efficacy endpoints are still being collected and will be summarized at the time of the study closing:

- Secondary Endpoint of Final OS
- Post-progression exploratory endpoints (PFS2, time to first subsequent anticancer treatment, time to second subsequent anticancer treatment, and chemotherapy-free interval)

The OS data were heavily censored at the time of the primary endpoint analysis. In order to adjust for multiple analyses of OS at a later stage, a stopping rule will be applied. The Haybittle-Peto[55, 56] stopping rule will be applied, where an OS result with a p-value < 0.001 can be used to claim superiority of rucaparib compared to placebo. This means that a p-value < 0.05 can be utilized at the final analysis, which is projected to occur once 70% of the death events have been collected.

11.4 Sample Size Considerations

The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious tBRCA mutation will be enrolled. Enrollment of patients with a known deleterious gBRCA mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA, which will evaluate homologous recombination gene mutations and/or extent of genomic scarring in tumor tissue.

Table 4 below provides estimated sample sizes and power calculations.

Table 4. Estimated Sample Sizes and Power Calculations

Group	Hazard Ratio	Cumulative N	Minimum Number of Events (70%)	Median PFS Placebo vs Rucaparib (months)	Power	One-sided Alpha
BRCA HRD	0.50	180	126	6 vs 12	90%	0.025
All HRD (BRCA + nbHRD)	0.60	300	210	6 vs 10	90%	0.025
ITT Population (BRCA + nbHRD + Biomarker Negative)	0.70	540	378	6 vs 8.5	90%	0.025

The study will end after 70% of the patients in the tBRCA subgroup have an observed event of investigator-determined disease progression or death. If the minimum number of tBRCA patients are enrolled, then the study will end following the 126th event of investigator-determined disease progression or death. Similarly, if the maximum number of tBRCA patients are enrolled, then the study will end following the 140th event of investigator-determined disease progression or death. The IDMC will inform the sponsor when the required number of PFS events have been observed in order to ensure the sponsor remains blinded to which patients are in the tBRCA subgroup. If the nbHRD and/or biomarker negative subgroups have observed events of invPFS in fewer than 60% of the patients, the IDMC may recommend that the study continue for up to 6 more months if it is likely that the nbHRD and biomarker negative subgroups will observe enough additional events of PFS to reach 60%.

Following the collection of the required number of PFS events, the outstanding queries for all visits and events prior to the data cutoff date will be resolved and the database will be locked before the blind break and subsequent primary analysis.

12 PATIENT DISPOSITION

12.1 Removal of patients from therapy or assessment

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

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator
- 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.

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

12.2 Procedures for discontinuation

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

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

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

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

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

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

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

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

13.2 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 begin study-specific screening until appropriate regulatory approval of the study protocol has been received.

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

The study will be registered on regionally-relevant registries, including www.clinicaltrials.gov, EU Clinical Trials Register, and other applicable trial registry systems as appropriate. Data generated from this study must be handled in accordance with any laws, rules, and regulations

related to the privacy of personal data or medical information applicable in the jurisdiction where the data is processed, including without limitation, the US Health Information Portability and Accountability Act of 1996 (HIPAA), and its implementing regulations, and the European Union General Data Protection Regulation 2016/679 (GDPR).

13.2.1 Institutional Review Board or Independent Ethics Committee Approval

The protocol, all protocol amendments, and any material to be provided to the patient (such as the ICF, Patient Information Sheets (PIS), advertisements, drug dosing diaries, or descriptions of the study used to obtain informed consent) must be reviewed and approved by an IRB/IEC before study start, according to national law and/or local regulations. There must be proof of submission of the Investigator's Brochure (IB) to the IRB/IEC. The sponsor will supply relevant information to the investigator to use for submission of the study protocol and additional study documents to the IRB/IEC. Verification of the IEC's/IRB's unconditional approval of the study protocol and the written ICF will be transmitted to Clovis Oncology by the investigator or by other means as determined between the investigator and the sponsor.

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

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

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

13.3 Patient Information and Informed Consent

13.3.1 General Aspects of Informed Consent

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

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

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

13.3.2 Informed Consent Process

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

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

13.3.3 Additional Informed Consent Documentation

Patients providing an optional tumor tissue biopsy sample at the time of radiographic disease progression/treatment discontinuation must consent to this procedure. A separate consent form may be used for tissue testing.

13.4 Patient Confidentiality

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., no names or, in some regions, initials or date of birth) according to country regulations will be recorded on any form submitted to the sponsor and the IEC/IRB. The investigator must have a list where the identity of all treated patients can be found, but not intended for use by the sponsor.

13.5 Study Monitoring

The sponsor, or contract research organization (CRO) or contract monitor acting on the sponsor's behalf, will contact or visit the investigator at the study center prior to the entry of the first patient (unless the sponsor or the CRO has worked with the center recently in the same or comparable indication, the site location and facilities have not changed significantly since after the last visit by the sponsor or CRO, and the potential investigator/site are currently in good standing with respect to regulatory compliance, in which case this initial visit may be waived) and at predetermined appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit.

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

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

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

13.6 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.

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

All source documents should be completed in a neat, legible manner according to the principles of Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and ‘Plus’ (+) Complete, Consistent, Enduring, and Available (ALCOA+), to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

Prior to study start, the investigator will prepare a list showing the all individuals delegated responsibility on this study. This “study site personnel and delegation list” must be kept current throughout the study.

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.

Data collection will be decreased at the time of implementation of Protocol Amendment 5, as all endpoints except those associated with long-term follow up have been met and reported. As of

the implementation of Protocol Amendment 5, the assessments required to be entered into the study eCRFs/eCRF modules for patients are as follows:

- Log Forms
  - Adverse Events (SAE/AESIs only)
  - Subsequent Anticancer Therapy (SAT)
- TA_Scan
- EOT
- 28-Day Post
- Long-Term Follow-Up
- Death
- PI_Sign

Updated eCRF Completion Guidelines will be provided to the sites for further detail regarding what should be entered for patients that are ongoing on treatment or in long-term follow-up at the time Protocol Amendment 5 is implemented.

13.7 Study Termination and Site Closure

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

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

The entire study will be stopped if any of the following applies:

- The protocol-specified treatment is considered too toxic to continue the study;
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical;
- The stated objectives of the study are achieved; or
- The sponsor discontinues the development of 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 in source documents and on the eCRF. All reasons for discontinuation of treatment must be documented.

If the study is terminated prematurely the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The investigators will promptly inform their

IRB/IEC, providing the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

13.8 Study Protocol Amendments

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

13.9 Retention of Study Documents

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

The sponsor and investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version, history, search, and retrieval. The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study specific source documents, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable inspections or audits from regulatory authorities, the IRB/IEC, and the sponsor or its designees. The investigator shall retain records and documents, including signed ICFs, pertaining to the conduct of the study for a period of 25 years after study completion or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents will be retained for a longer period if required by the applicable regulatory requirement(s), institutional policies, 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. Copies of original documents will fulfill the ICH E6(R2) requirements for certified copies. 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.

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

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

13.10 Quality Control and Assurance

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

13.10.1 Protocol Deviations

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

13.10.2 Study Site Training

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

13.10.3 Quality Assurance Audits and Inspections

An audit of a clinical center may be conducted by a quality assurance auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. IRB/IEC representatives may also conduct an audit of the study at any time.

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

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

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

13.11 Clinical Study Report

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

13.12 Study Publication and Disclosure Policy

All information for the study provided by the sponsor or designee to the investigator, including, but not limited to, the IB, this protocol, eCRFs, the protocol-specified treatment, and any other study information, will remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without 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.

All data generated from this study will be maintained by the sponsor. All data generated from this study, and all information furnished by the sponsor, the investigators, and other participating study groups shall be held in strict confidence. Independent analysis and/or publication of study data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICMJE]).[57] Written permission to the investigator will be contingent on the review of the statistical analysis and manuscript/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 60 days prior to submission. This timeframe will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

13.13 Investigator Oversight

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

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15 APPENDICES

15.1 Appendix A

List of Homologous Recombination Genes for HRD Stratification by the ICTA

tBRCA	nbHRD		Biomarker-negative
BRCA1	ATM	FANCI	Genes not included in the tBRCA or nbHRD groups
BRCA2	ATR	FANCL	
	ATRX	FANCM	
	BARD1	MRE11A	
	BLM	NBN	
	BRIP1	PALB2	
	CHEK1	RAD50	
	CHEK2	RAD51	
	FANCA	RAD51B	
	FANCC	RAD51C	
	FANCD2	RAD51D	
	FANCE	RAD52	
	FANCF	RAD54L	
	FANCG	RPA1	

15.2 Appendix B

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (v1.1) are described in Eisenhauer (2009)[33] 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 n 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.

Non target 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 progressive disease (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			
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

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
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 complete response (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 at screening and at the end of every 3rd cycle of treatment.

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.

15.3 Appendix C

Modified Gynecological Cancer Intergroup (GCIG) Guidelines

GCIG Guidelines for Response Using CA-125[34] (adapted for use in this trial)

GCIG CA-125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires at least one pre-treatment sample >2 x ULN and two post-treatment samples confirming a response

A response to CA-125 has occurred if there is at least a 50% decrease as the result of the treatment. The pre / post treatment samples must satisfy the following criteria:

1. There must be at least one sample that is >2 x ULN prior to initiation of treatment
2. The second sample (post-treatment) must be ≤ 50% of the pre-treatment sample;
3. The confirmatory third sample must be ≥21 days after the second sample and ≤ 110% of the second sample;
4. Any intervening samples between samples 2 and 3 must be ≤ 110% of the previous sample unless considered to be increasing because of tumor lysis.

Per inclusion criteria #5, CA-125 must =be <ULN prior to study entry. This requirement applies to all patients, including those who achieved a best response of PR by serologic CA-125 response criteria. Thus, patients must have achieved a >50% reduction in CA-125 level and also have CA-125 <ULN.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

15.4 Appendix D

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

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

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

15.5 Appendix E

National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy (NCCN-FACT) FACT - Ovarian Symptom Index (FOSI-18) instrument (NCCN-FACT FOSI-18) – English Version

Sample form and background available at: http://www.facit.org/FACITOrg/Questionnaires.

Patients will complete the instrument on an electronic device. This device is a Class 1 listed (i.e., approved) device.

Below is a list of statements that other people with your illness have said are important.

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
	BMT5	I am able to get around by myself	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4

GF7	I am content with the quality of my life right now	0	1	2	3	4

Euro-QoL5D (EQ-5D) – English Version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

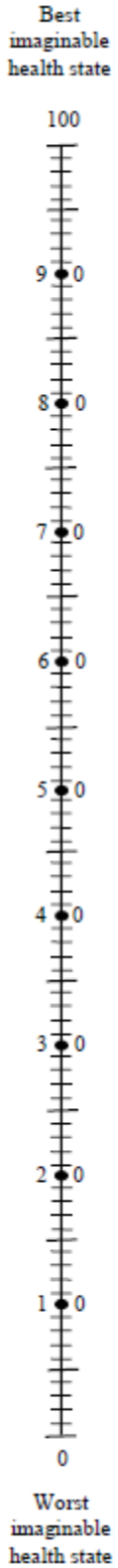
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



15.6 Appendix F

Examples of CYP Substrates with Narrow Therapeutic Range

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

The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012.[50]

[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).