CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209115Orig1s000

MULTI-DISCIPLINE REVIEW
Summary / Clinical / Non-Clinical

1 NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209115
Priority or Standard	Priority
Submit Date(s)	June 23, 2016
Received Date(s)	June 23, 2016
PDUFA Goal Date	February 23, 2017
Division/Office	DOP1/OHOP
Review Completion Date	November 22, 2016
Established Name	Rucaparib
(Proposed) Trade Name	RUBRACA
Pharmacologic Class	Poly (ADP-Ribose) Polymerase 1 inhibitor
Code name	AG-014669, PF-01367338,
Applicant	Clovis Oncology, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	600 mg PO BID
Applicant Proposed Indication(s)/Population(s)	Rubraca is indicated as monotherapy treatment of advanced ovarian cancer in patients with deleterious *BRCA*-mutated tumors, inclusive of both germline *BRCA* and somatic *BRCA* mutations (as detected by an FDA approved test), and who have been treated with two or more chemotherapies.
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics

PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Rucaparib (RUBRACA™) is a new molecular entity that is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair.

The Applicant's proposed indication at the time of NDA submission was:
Rubraca™ is indicated as monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline BRCA and somatic BRCA mutations (as detected by an FDA approved test), and who have been treated with two or more chemotherapies.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The recommended indication is:
Rubraca is indicated as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA approved companion diagnostic for Rubraca.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The recommended dose for rucaparib is 600mg orally twice daily with or without food. Treatment should be continued until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the accelerated approval of rucaparib, according to 21 Code of Federal Regulations (CFR) 314.510 Subpart H, is primarily based on efficacy data from 106 patients with deleterious *BRCA* mutation associated advanced ovarian cancer who have been treated with two or more chemotherapies, and safety data from 377 ovarian cancer patients, treated on two open-label, single arm trials (Study 10 and ARIEL2). A next-generation sequencing tissue companion diagnostic (CDx) to detect germline and/or somatic *BRCA*1 and/or *BRCA*2 mutations is being contemporaneously recommended for approval by the Center for Devices and Radiologic Health (CDRH). The investigator-assessed objective response rate (ORR) of 54% (95% CI: 44, 64) observed in the 106 patients and the supportive 9.2 month duration of response (DOR) are considered reasonably likely to predict clinical benefit. In addition, the safety profile is acceptable for the intended population and supportive of a

favorable benefit-risk profile of monotherapy rucaparib. All disciplines were in agreement with accelerated approval of rucaparib, or did not identify any outstanding issues that precluded approval. In summary, rucaparib for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies demonstrates a favorable benefit-risk profile with enough evidence to recommend accelerated approval. Continued approval for the indication may be contingent upon verification and description of clinical benefit in the confirmatory trials ARIEL3 and ARIEL4.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor recommended for accelerated approval as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. It is also recommended that the indication reflect that patients be selected for therapy based on an FDA-approved companion diagnostic for rucaparib.

Advanced ovarian cancer is a serious and life-threatening disease. Patients are treated early in their disease course with surgery and platinum doublet chemotherapies; however, as treatment lines progress, responses and duration of responses decrease and the disease is not curable. Patients with platinum-sensitive disease and patients with platinum-resistant or refractory disease can be treated along differing paradigms. In patients still platinum-sensitive (demonstrating a greater than 6 month response to last platinum) after two or more chemotherapies, response rates to standard platinum containing chemotherapy are generally 38-45%. Platinum-resistant disease (demonstrating less than 6 month response to last platinum) is generally less responsive to chemotherapy (with or without bevacizumab) with response rates ranging from 10-53% depending on chemotherapy and line of therapy. No available therapy exists for the specific *BRCA*m population after two or more chemotherapies, and all of the comparative chemotherapy and bevacizumab plus chemotherapy response information is not specific to a *BRCA*m population.

The effectiveness of rucaparib was demonstrated in 106 patients with deleterious *BRCA* mutation associated advanced ovarian cancer who have been treated with two or more chemotherapies on two single-arm open-label trials. All 106 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) as assessed by the investigator was 54% (95% CI: 44, 64) with 9% complete responses and 45% partial responses. Median duration of response was 9.2 months (95% CI 6.6, 11.6). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a *BRCA1* gene mutation or *BRCA2* gene mutation. Tumor *BRCA* mutation status (including germline and/or somatic *BRCA* mutations) was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the recommended companion diagnostic (CDx) FoundationFocus CDx *BRCA*™ test. Despite uncertainty regarding the direct clinical benefit of ORR, in patients with *BRCA*-mutated (germline and/or somatic) advanced ovarian cancer that have been treated with two or more lines of chemotherapy, the benefit of this oral monotherapy to result in tumor response for multiple months is considered reasonably likely to predict clinical benefit, and uncertainty is mitigated by the accelerated approval pathway and verification of benefit in confirmatory studies. In addition, an ORR of 54% (and 66% in platinum-sensitive patients), is considered better than available therapy response rates patients with deleterious *BRCA*m advanced ovarian cancer after two or more chemotherapies.

The most common adverse reactions (AR) experienced in at least 20% of the 377 patients with advanced ovarian cancer treated with rucaparib and included in the safety population were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Discontinuations due to AR occurred in 10% of patients however no one AR except for fatigue/asthenia (2.4%) accounted for more than 2% of discontinuations. Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) were the most concerning ARs identified, but only occurred in two (0.5%) of the patients in the safety population. Labeling adequately describes and conveys the AML/MDS concern in the Warnings and Precautions section, and no further mitigation strategy such as a REMS is recommended. In general, the safety profile of rucaparib was tolerable compared to alternative chemotherapy (with or without bevacizumab) options, as evidenced by no boxed warnings and inclusion of only one AR in the warnings and precautions section of rucaparib labeling.

Overall, rucaparib, an oral monotherapy with a biologic and mechanistic rationale for use in a subpopulation of patients, demonstrated an ORR, with supportive DOR, reasonably likely to predict clinical benefit in a genomic subset of patients who have a refractory, advanced, life-threatening, and unmet medical need malignancy. The safety profile is acceptable in the population indicated and provides an alternative toxicity profile, and the potential for patients to be treated with an effective monotherapy while delaying the repeated and cumulative toxicity of chemotherapy, chemotherapy combinations, or chemotherapy plus bevacizumab. In addition, there was a consistent recommendation for approval, or no outstanding issues to preclude approval, from all disciplines. A CDx will be approved contemporaneously with rucaparib and provide information essential for the safe and effective use of rucaparib. The benefit-risk profile is favorable to support accelerated approval of rucaparib as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Continued approval for the indication may be contingent upon verification and description of clinical benefit in the confirmatory trials ARIEL3 and ARIEL4. The applicant agreed to the conduct and submission of results from these studies as post-marketing requirements under accelerated approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 14,000 deaths occur in the U.S. from advanced ovarian cancer each year. • Patients with advanced ovarian cancer following two or more chemotherapies carry a poor prognosis. • Patients with deleterious *BRCA* associated (germline and/or somatic) ovarian cancer represent a unique population with defects in homologous recombination pathway genes.	**Advanced ovarian cancer is a serious and life-threatening disease. There is a significant unmet medical need to develop therapies for advanced ovarian cancer. Certain therapies can exploit defects in the homologous recombination pathway.**
Current Treatment Options	• There are no available therapies specifically for patients with *BRCA*m ovarian cancer who have received two or more chemotherapies. • Independent of *BRCA* status, chemotherapies or chemotherapy plus bevacizumab are standard of care in patients who have received two or more chemotherapies. Choice of therapy depends of platinum-sensitivity status. Response rates vary from 10-50% depending on line of therapy and platinum sensitivity status. • Available chemotherapies and chemotherapy plus bevacizumab are toxic regimens.	**Patients with *BRCA* mutation associated advanced ovarian cancer may have a different natural history of disease and could benefit from a safe and effective oral monotherapy after two or more chemotherapies.**
Benefit	• Of the 106 patients with *BRCA*m advanced ovarian cancer who had received two or more chemotherapies, ORR was 54% (95% CI: 44, 64) and DOR was 9.2% (91% CI: 6.6, 11.6). • Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. • Tumor *BRCA* mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the FoundationFocus CDx *BRCA*™ test.	**Evidence of effectiveness was supported by an ORR with supportive DOR that is reasonable likely to predict clinical benefit. The FoundationFocus CDx *BRCA*™ test is recommended for selection of patients for safe and effective use of rucaparib and will detect germline and/or somatic mutations but cannot distinguish between the two. Uncertainty of the true clinical benefit of rucaparib, in the context of the known safety profile, is acceptable based on the nature of incurable advanced ovarian cancer as a serious and life-threatening disease with limited treatment options in accordance with the principles described in 21 CFR 314, Subpart H.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• Tolerated with most common adverse reactions (AR) (≥ 20%) were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. • 10% dose discontinuation due to ARs, only fatigue resulted in greater than a 2% dose discontinuation rate at 2.4%. • AML/MDS risk is clinically significant but was low (0.5%).	**The overall safety profile of rucaparib is acceptable for the intended population. AML/MDS is the only AR being described in the warnings and precautions section of labeling. In comparison with other available therapies, the safety profile is potentially improved and represents an alternative monotherapy option to patients with *BRCA*m tumors.**
Risk Management	• Rucaparib is intended to be prescribed by oncologists. • Oncologists are well versed in the identification and management of the toxicities associated with rucaparib. • Labeling for AML/MDS in Warnings and Precautions. • Accelerated approval based on ORR and DOR.	**The safe use of rucaparib can be managed through accurate labeling and routine oncology care. No REMS is indicated. Confirmatory trials (ARIEL3 and ARIEL4) are ongoing to verify clinical benefit.**

2 Therapeutic Context

Analysis of Condition

Ovarian cancer continues to be the fifth leading cause of cancer deaths in women in the United States, with an expected 22,280 cases diagnosed and 14,240 deaths this year (American Cancer Society, 2016). Because there are no validated screening tools for the early detection of ovarian cancer, the disease is often diagnosed at an advanced stage, requiring surgical debulking followed by standard-of-care chemotherapy treatment with platinum and a taxane for six to eight cycles. While this up-front treatment can result in no evidence of disease in most women, up to 80% will experience recurrence, and the timing of this recurrence predicts sensitivity of the disease to subsequent chemotherapy. No proven therapy is available for women with the poorest prognosis—those with disease that progresses during initial platinum therapy, known as platinum-refractory disease. Patients whose disease relapses in less than six months are considered platinum resistant, and for these women, few treatment options have demonstrated benefit. For women whose disease relapses later than six months from the end of treatment—considered platinum sensitive—repeat courses of platinum-containing regimens, with their attendant and often cumulative toxicities, are effective until the inevitable emergence of platinum resistance. The duration of response to platinum is also correlated with the efficacy of subsequent platinum-based treatment.

The genes *BRCA1* and *BRCA2* are two of several genes known to encode proteins critical for the repair of double strand breaks through the homologous recombination (HR) pathway, along with other functions that maintain genomic integrity. Deleterious germline *BRCA1* and *BRCA2* mutations are known to confer increased risk of breast and ovarian cancer, and an estimated 10-15% of all U.S. ovarian cancer patients carry germline *BRCA* mutation (g*BRCA*m). Prior to the 2014 approval of olaparib, an inhibitor of poly (ADP-ribose) polymerase (PARP), women with g*BRCA*m ovarian cancer were treated under the same paradigm as women with *BRCA*wt ovarian cancer, but epidemiologic evidence suggests they have improved survival, likely due to increased and prolonged chemotherapy sensitivity. Olaparib has received marketing approval for the treatment of women with g*BRCA*m ovarian cancer after three prior chemotherapy regimens.

The hundreds of known deleterious *BRCA*1/2 mutations are accompanied by an unknown number of other genetic alterations, such as mutation of RAD51, that may lead to disruption of HR function (denoted homologous recombination deficient, HRD). Cells that are functionally HRD are reliant on other DNA repair mechanisms to maintain genomic integrity, such that inhibition of one of these other pathways may lead to cell death via synthetic lethality. One such mechanism, base excision repair (BER), relies on the protein PARP1; inhibition of PARP1 via small molecules results in the accumulation of double-strand breaks and subsequent cell death.

While germline *BRCA* mutations have been under investigation since the identification of the gene and the cancer association in 1994, less is known about sporadic, somatic *BRCA* mutation that may occur in ovarian cancer tissue, which requires diagnosis by sequencing DNA extracted from tumor specimens. Because these tumors would putatively also be homologous recombination deficient, tumors bearing these somatic mutations (denoted s *BRCA*m), found in 6%-8% of ovarian cancers (TCGA, Nature, 2011) should be susceptible to the same targeted treatment strategy.

2.2. Analysis of Current Treatment Options

There are no available therapies specifically for patients with deleterious *BRCA*m advanced ovarian cancer. Olaparib received accelerated approval in 2014 for the treatment of g*BRCA*m ovarian cancer (not s *BRCA*m ovarian cancer) in women who have received three prior lines of chemotherapy. Although olaparib is approved under accelerated approval, it is not considered available therapy (FDA Guidance for Industry- Expedited Programs for Serious Conditions—Drugs and Biologics May 2014). No agents are currently approved under regular approval or accelerated approval for the specific treatment of women with s*BRCA*m, or *BRCA*m following two chemotherapy regimens. Several agents are commonly used for treatment of women with ovarian cancer (regardless of *BRCA* status) in the third line, both on- and off-label (See Table 1).

No trials are available for evaluation that study third-line efficacy in the *BRCA*m ovarian cancer population, though this group appears to have the advantage of increased chemosensitivity leading to longer durations of response and survival based on epidemiologic data. Studies evaluating the application of chemotherapy in the third-line ovarian cancer setting have generally followed the classical clinical convention of dividing patients into platinum-sensitive and platinum-resistant/refractory subgroups; extrapolating to an “all-comers” cohort is difficult given the markedly varied natural histories of these diseases.

Response to platinum is thought to predict chemosensitivity and outcomes; the longer a patient remains progression-free following platinum, the higher the chance of surviving and continuing to respond. Standard treatment for third-line, platinum-sensitive ovarian cancer (a population in the CALYPSO study, Pujade-Laurraine, JCO, 2010) reports response rates of 39-45% for patients progression-free for 6-12 months after platinum, vs. 38-42% for patients with post-platinum progression after 24 months. *BRCA* mutation status of these patient populations is unknown, and so extrapolation of these data is difficult for the current population.

In patients with platinum-resistant disease, response rates in the AURELIA study (enrolling patients with $\leq$2 prior lines of therapy) were 28% (95% CI: 21, 36) in the chemotherapy plus bevacizumab group (and 53% in the un-prespecified paclitaxel-bevacizumab subgroup); again, *BRCA* status is unknown in these patients, and so extrapolation to the patient population under study is not feasible.

Table 1: Agents for the Treatment of Women with Advanced Ovarian Cancer

Product (s) Name	Relevant Indication	Year of Approval	Administration	Efficacy Information [a]	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments of Women with g*BRCA*m Ovarian Carcinoma						
Olaparib[b]	Monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.	2014	400 mg PO BID	ORR in patients with measurable disease was 34% (95%CI: 26, 42) and median DOR of 7.9 months.	Around 2% of patients in pivotal trial developed MDS/AML, some pneumonitis; otherwise, well-tolerated with prolonged low-grade anemia, GI disturbance and fatigue	PARP inhibitor: same class of agents as the current compound.
FDA-approved Treatments for Women with Ovarian Carcinoma						
Cisplatin	Ovarian cancer	1978	IV	NA	Nephrotoxicity, neurotoxicity, emetogenic	NA
Cyclophospha-mide	Ovarian cancer	Pre-1984	IV		Myelosuppression	
Melphalan	Ovarian cancer	Pre-1984	IV			

Product (s) Name	**Relevant Indication**	**Year of Approval**	**Administration**	**Efficacy Information** [a]	**Important Safety and Tolerability Issues**	**Other Comments**
Altretamine	Ovarian cancer	1990	IV	RR: 18%		
Carboplatin	Ovarian cancer	1991	IV	NA	Myelosuppression	
Paclitaxel	Ovarian cancer	1992	IV	RR:[c] 15-20%	Neurotoxicity, infusion reactions	Studied in 2nd- 6th line of treatment
Topotecan	Ovarian cancer	1996	IV	RR: 21%	Myelosuppression	Studied in 2nd-line treatment
Pegylated Liposomal Doxorubicin	Ovarian cancer	1999	IV	RR: 18%	Myelosuppression	Data for g*BRCA*m patients from Study 12
Gemcitabine (plus carboplatin)	Ovarian cancer	2006	IV	RR: 47%	Myelosuppression	Studied in 2nd-line of treatment
Bevacizumab	Ovarian Cancer (platinum-resistant)	2014	IV	RR: 53%[d]	Thrombosis, wound healing, GI perforation	Studied in 2nd-3rd line of treatment
Other Agents Commonly Used for Ovarian Cancer						
Ifosfamide		1992	IV	RR: 12%		Studied in 2nd-3rd line of treatment
Etoposide		1998	IV	RR: 30%		Studied in 2nd-line treatment
Oxaliplatin		2000	IV	RR: 17%		Studied in 2nd-3rd line of treatment

Product (s) Name	Relevant Indication	Year of Approval	Administration	Efficacy Information [a]	Important Safety and Tolerability Issues	Other Comments
Tamoxifen		2001	PO	RR: 10%		
Docetaxel		2003	IV	RR: 22%		Studied in 2nd-3rd line of treatment
Irinotecan		2003	IV	RR: 17%		Studied in 2nd-3rd line of treatment
Vinorelbine		2004	IV	RR: 3%		Studied in 3rd-line of treatment
Letrozole		2007	PO	RR: 9%		Studied in 2nd-4th line of treatment

[a]: Data from Product Package Insert unless otherwise declared.

[b]: approved under accelerated approval and therefore not considered available therapy for the purposes of the accelerated approval pathway

[c]: RR=objective response rate

[d]: Taken from unplanned subgroup analysis in combination with paclitaxel

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Rucaparib is a new molecular entity that is currently not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following summarizes the important clinical presubmission regulatory activity for rucaparib:

- August 26, 2009: IND 106289 was opened by Pfizer Inc., with protocol A4991014, entitled, "A Parallel Arms Phase I Safety, Pharmacokinetic and Pharmacodynamic Study of the Intravenous Poly (ADP-Ribose) Polymerase (PARP) Inhibitor PF–01367338 (AG–014699) In Combination With Several Chemotherapeutic Regimens in Adult Patients With Advanced Solid Tumor."
- September 11, 2011: IND sponsorship transferred from Pfizer Inc. to Clovis Oncology, Inc.
- July 31, 2012: Orphan Drug Designation granted for rucaparib for the treatment of ovarian cancer.
- August 3, 2012: Type C meeting for guidance on rucaparib development strategy. (b) (4) During this meeting, FDA stated that the sponsor would be required to have an approved test for deleterious *BRCA*1 and 2 mutations at the time of the proposed approval of rucaparib, and recommended using the marketed test to select patients for the studies, or to have a clinical validation plan. The sponsor was advised to perform *BRCA* testing on all enrolled patients, that response rate should be of sufficient magnitude to provide meaningful therapeutic benefit, and that the confirmatory study should be underway at the time of approval. (b) (4) At this meeting, Clovis proposed a staged approach to companion diagnostic development, with blood *BRCA* testing to be confirmed at a central laboratory, with further diagnostic development to be focused on a tissue-based assay. The sponsor was told that a sample size of about 100 patients had been required in a rare disease setting to support approval, but that the final number would be a review issue.
- December 14, 2012: Type C meeting for guidance to discuss changes to clinical study CO-338-014, the proposed confirmatory study for accelerated approval of rucaparib in t*BRCA*m ovarian cancer. The trial was modified to include all patients stratified by homologous recombination deficiency (HRD) score in tumor tissue developed as a companion diagnostic device, with primary endpoint of investigator-assessed progression-free survival, and stratified by HRD classification, platinum-free interval, and best response to preceding platinum, with a sample size of 500 patients.

- May 6, 2014: Type C meeting to address sponsor questions regarding the development of the companion diagnostic device in development for determining HRD status among enrolled patients, specifically the development of the cutoff for scoring patients HRD+ vs HRD-, which the sponsor proposed to perform post-randomization. Discussion also took place regarding (b) (4) Suitability of the proposed HRD clinical trial assay (CTA) for premarket authorization (PMA) submission was discussed and found to be suitable for CDRH review after detailed device and validation plans were available.
- November 4, 2014: End of Phase 2 Meeting: agreement that the design and planned analyses of Studies CO-338-010 and CO-338-017 were adequate to address the objectives necessary to support a regulatory submission. Included in this agreement was the use of objective response rate (ORR) as the primary efficacy outcome and duration of response as a secondary endpoint. Also discussed was the need for concurrent approval of the companion diagnostic device at the time of approval of rucaparib. FDA suggested to the sponsor that they submit a PMA for a component of the initially proposed HRD assay with a focus on the t *BRCA* status.
- April 3, 2015: Breakthrough Therapy Designation granted for rucaparib for monotherapy treatment of advanced ovarian cancer in patients who have received at least two lines of prior platinum-containing therapy, with *BRCA*-mutated (t *BRCA*m) tumors, inclusive of both germline *BRCA* (s *BRCA*m) and somatic *BRCA* (s *BRCA*) mutations.
- August 20, 2015: Type C meeting to discuss the HRD test and performance of rucaparib in patients at various HRD+ cutoffs. At this time, the response rate for patients in the " *BRCA*-like" HRD+ subgroup who had had $\geq$2 prior chemotherapy regimens was below 20%, which FDA informed the sponsor was not superior to available therapy in the platinum sensitive population. FDA agreed that patients who had been treated with $\geq$ 2 platinum-based doublets could be an appropriate patient population for a marketing application. CDRH was present for this meeting and confirmed for the sponsor that the diagnostic device in development is consistent with a non-significant risk study.
- April 4, 2016: A type B, pre-NDA meeting was held with the sponsor to discuss the planned content, format, and timeline for the rolling NDA for accelerated approval of rucaparib. Agreement was reached regarding the number of patients in the primary efficacy population, as well as the safety population to be included in the integrated summary of safety.

The following summarizes the important clinical post-submission regulatory activity for rucaparib:

- October 27, 2016: Teleconference with the applicant to discuss the inclusion of g *BRCA*m and s *BRCA*m patients in the indication for rucaparib. An agreement was reached to conduct a post-marketing commitment to develop an FDA-approved test that identifies g *BRCA*m ovarian cancer patients, as the companion diagnostic device for concurrent approval does not distinguish between germline and somatic mutations.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 1 (DOP1) consulted the Office of Scientific Investigation (OSI) to perform an audit of four clinical trial sites (site #20/14001 Dr. Amit Oza, Princess Margaret Hospital, Toronto, Canada; site #14002 Dr. Anna Tinker, BC Cancer Agency, Vancouver, Canada; Site #32005 Dr. Robert Coleman, MDACC, Houston, TX; and #32002, Dr. Carol Aghajanian, MSKCC, New York, NY), the applicant site, Clovis Oncology, Inc., to identify any issues that could affect the quality and interpretation of the data submitted with this application regarding clinical studies CO-338-010 (Study 10) and CO-338-017 (ARIEL2). The Division, in consultation with OSI, selected clinical sites for inspection based on enrollment characteristics and patterns of efficacy reporting. The inspections of Drs. Oza, Tinker, Coleman, and Aghahanian, and Clovis Oncology, Inc., found no significant deficiencies, associated with Study CO-338-010 (Study 10) and Study CO-338-017 (ARIEL2) conduct. The data from Study 10 and ARIEL2 appear reliable.

4.2. Product Quality

See the FDA CMC review by Xing Wang, PhD for further details. Per the CMC reviewer, there were no identified CMC deficiencies. All excipients are compendial grade. The proposed drug product specification is deemed adequate to assure identity, strength, purity, and quality of the drug product. Based on review of stability data, the proposed expiration period of 24 months will be granted provided that the drug product is packaged in the proposed packaging configuration and storage conditions.

Novel excipients: No
Any impurity of concern: No

4.3. Clinical Microbiology

See the FDA product quality review for details. Per the reviewer's assessment, and after response to a request for information, the reviewer concluded that the presented data were acceptable.

4.4. Devices and Companion Diagnostic Issues

The applicant, Clovis Oncology, Inc., has partnered with Foundation Medicine, Inc., to develop the next-generation sequencing (NGS)-based companion diagnostic device FoundationFocus CDx *BRCA*™ for detection of *BRCA*1 and *BRCA*2 alterations, inclusive of both germline and somatic alterations, in DNA extracted from patient tumor specimens. The companion device is intended to be used to select patients for whom treatment with rucaparib may be indicated. The assay applies a computational

algorithm to detect sequence alterations in *BRCA*1/2 genes; when identified, patients with these *BRCA*1/2 alterations may be eligible for rucaparib treatment. This device is under review at the Center for Diagnostics and Radiological Health (CDRH) under PMA 160018 and is planned to be approved contemporaneously with rucaparib.

The device is intended to detect *BRCA*1/2 alterations in formalin-fixed, paraffin-embedded (FFPE) tumor tissue, and therefore should detect both germline and somatic alterations; however, this device does not adjudicate the source of the mutation as germline or somatic. In discussion with the applicant, agreement was reached regarding a post-marketing commitment to provide clinical and scientific validation of a companion diagnostic device capable of detecting germline *BRCA* (b) (4)

BRCA status in ARIEL2 was determined using a number of different methods, and responses to information requests and discussion at the midcycle meeting were required in order to develop a fuller understanding of the use of the companion diagnostic device during its development in the trials. The methods employed include: a local test result reported in the patient's medical record; the tissue-based clinical trial assay (CTA) performed centrally by Foundation Medicine, Inc. (FM), which includes the exploratory inference determination; and the BROCA test (a blood based test) which can determine germline *BRCA* mutations. Of these, the inference method of the CTA is considered exploratory and the BROCA test is considered definitive for determination of germline or somatic. Patients for whom sufficient tumor DNA was available after the CTA was performed also had retrospective testing using the companion diagnostic. Tumor *BRCA* mutation was verified retrospectively in 96% (64/67) of the patients for whom tumor tissue-extracted DNA samples were available.

Somatic *BRCA* alterations were adjudicated using a stepwise process: patients with t *BRCA*m by the FMI CTA, and normal germline testing using the NGS BROCA blood-based assay performed at (b) (4) were considered to have s *BRCA*m. Using this process, the applicant reported that 18 patients (18/106, 17%) had somatic mutations in *BRCA*1/2.

The PMA under review for the FMI companion diagnostic is due to be completed as of the date of approval of rucaparib and the device is planned for contemporaneous approval.

5 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drugs Advisory Committee (ODAC) for this NDA as there were no safety or efficacy issues identified for the proposed indication that required outside advice.

6 Pediatrics

Rucaparib has not been studied in a pediatric population. The orphan designation status exempted the applicant from PREA Requirements.

7 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is indicated for the proposed indication.

7.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable

7.2. Conditions of Use to Address Safety Issue(s)

Not applicable

7.3. Recommendations on REMS

Not applicable

8 Postmarketing Requirements and Commitments

The FDA review team identified the following postmarketing requirements (PMR) and postmarketing commitments (PMC) for the recommended accelerated approval. These requirements and commitments have been agreed upon by the Applicant.

PMRs:
The clinical PMRs are related to requirements accelerated approval requirements. Confirmatory trial(s) are required to confirm the clinical benefit for drugs approved under subpart H (505(b) of the Federal Food, Drug, and Cosmetic Act). There are also two clinical pharmacology PMRs related to drug-drug interactions and hepatic dose.

1. Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial CO-338-043 entitled "A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, *BRCA* Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer," (ARIEL4).

Final Protocol Submission (ARIEL4):	Submitted 6/20/2016
Interim Report Submission (PFS analysis):	12/2022
Trial Completion:	6/2024
Final Report Submission (OS analysis):	12/2024

2. Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial CO-338-014 entitled, "Phase 3 Study of Rucaparib as Switch Maintenance After Platinum in Relapsed High Grade Serous and Endometrioid Ovarian Cancer" (ARIEL3).

Final Protocol Submission (ARIEL3):	Submitted 9/09/2013
Interim Report Submission (PFS analysis):	3/2018
Trial Completion:	9/2020
Final Report Submission (OS analysis):	3/2021

3. Complete the ongoing drug-drug interaction trial CO-338-044 and submit the final study report. Timelines are under discussion at the time of this review.

4. Conduct a dedicated PK study in patients with moderate hepatic impairment to determine the appropriate starting dose in patients with moderate hepatic impairment.
Timelines are under discussion at the time of this review.

PMCs:

1. Submit to FDA the appropriate analytical and clinical validation of a companion diagnostic test that will enable the evaluation of patients' germline *BRCA* status.

Final Protocol Submission:	6/2017
Trial Completion	9/2017
Final Report Submission:	3/2018

2. Submit the final study report of ongoing mass balance trial CO-338-045.Timelines are under discussion at the time of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANJEEVE BALASUBRAMANIAM
11/22/2016

JULIA A BEAVER
11/22/2016

9 Nonclinical Pharmacology/Toxicology

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9.1. Executive Summary

Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. In vitro, rucaparib inhibited several enzymes in the PARP family, but it showed the strongest inhibitory activity towards PARP-1, PARP-2, and PARP-3. PARP enzymes are involved in cellular homeostasis, including DNA transcription, cell cycle regulation, and DNA repair. In the absence of PARP activity, unrepaired DNA single strand breaks can lead to more deleterious double strand breaks, which require other repair mechanisms, such as homologous recombination or non-homologous end joining. A deficiency in BRCA, which is involved in homologous recombination, would cause further DNA damage leading to cell death. This is the main rationale supporting the proposed indication and use of rucaparib in patients with deleterious BRCA mutations.

Data from in vitro pharmacology study reports submitted to this NDA showed that rucaparib-induced cell death was correlated with upregulation of apoptotic markers, decreased PAR formation (a pharmacodynamic marker of PARP inhibition), and increased DNA damage. Increased cytotoxicity was observed in tumor cell lines containing deficiencies in BRCA compared with cell lines with wild type BRCA. A literature reference was also provided to support the similarity of the proposed mechanism of action of rucaparib to other PARP inhibitors such as the FDA-approved Lynparza (olaparib), including data from studies aimed at assessing trapping of PARP-DNA complexes. Rucaparib showed anti-tumor activity in mouse xenograft models of human cancers with or without BRCA deficiencies. Dose-related anti-tumor activity was correlated with levels of rucaparib in the plasma and tumor, and decreased PAR levels in tumor samples. The approved Established Pharmacologic Class (EPC) of “poly (ADP-ribose) polymerase (PARP) inhibitor” is applicable to rucaparib based on its pharmacological activity.

A standalone GLP-compliant safety pharmacology study was conducted to evaluate the effect of rucaparib on the nervous system in rats. In Sprague-Dawley rats, severe clinical signs and death were observed at 75 mg/kg IV and decreased motor activity was observed at 50 mg/kg. No adverse neurological adverse findings were observed at 15 mg/kg, which resulted in systemic exposure of approximately 1.8 times the human exposure (C_{max}) at the recommended dose.

Several secondary pharmacology studies were conducted to evaluate the potential of rucaparib to inhibit off-target receptors, enzymes, and channels. In enzymatic screening assays, rucaparib showed antagonistic activity towards the non-selective sigma receptor and several kinases involved in the regulation of the cell cycle and survival/apoptotic pathways. In follow-up cellular assays, rucaparib did not inhibit PIM1, PIM2, or PIM3, which were the only three kinases evaluate in these assays. Inhibition of the other kinases identified in enzymatic screening assays as potential targets of rucaparib was not tested in cellular assays and cannot be ruled out.

Two human metabolites of rucaparib, M324 and M338, have been identified in patient plasma from preliminary studies at levels suggesting they may be major metabolites. The Applicant stated that M324 is a Phase I metabolite of rucaparib and M338 is a product of Phase II metabolic reaction of M324. Based on preliminary results, rucaparib, M324, and M338 account for approximately 43.5% to 55.1%, 16.8% to 20.0%, and 12.8% to 24.9%, respectively, of the total rucaparib-related molecules. M324 has been

identified as the only major metabolite in rats (up to 48.0% of total radioactivity in plasma) and dogs (up to 23.7% of total radioactivity in plasma), while M338 has not been observed in rat or dog plasma. At the time of this NDA submission, the Applicant had not conducted any further nonclinical studies with M338, based on the rationale that Phase II metabolic reactions generally render drugs less active pharmacologically and toxicologically. A definitive evaluation of rucaparib metabolites in patients will be conducted post-marketing in a human mass balance study. The need for additional studies to evaluate the pharmacokinetic and pharmacodynamic properties of M338 will be determined following submission and review of the human mass balance study.

Rucaparib was evaluated in GLP-compliant, repeat-dose general toxicology studies in rats and dogs with oral administration of up to 13 weeks in duration. The major target organs of toxicity in both rats and dogs were the bone marrow (hypocellularity and atrophy) and lymphoid organs (lymphoid depletion), which correlated with the major clinical pathology findings in animals of decreased red cell mass and decreased white blood cell counts. Additional findings resulting from rucaparib administration included decreased body weights and hemorrhage in the gastrointestinal tract. The dose of 75 mg/kg/day in a 4-week study in dogs was tolerable for the duration of the study, while 40 mg/kg/day in a 13-week study in dogs was not tolerable within the first month of the study. There is no clear explanation for this difference. Overall, the findings in animals were consistent with the hematological and gastrointestinal adverse reactions reported in patients treated with rucaparib. However, increases in alanine and aspartate transferases observed in patients were not observed in animal toxicology studies.

Rucaparib was mutagenic in a bacterial reverse mutation (Ames) test and clastogenic in an in vitro chromosomal aberration assay in cultured human lymphocytes. The clastogenic response in mitotically-stimulated cells was anticipated based on the mechanism of action of rucaparib and may suggest a potential increased risk for patients receiving rucaparib to develop secondary malignancies. Although myelodysplastic syndrome and acute myeloid leukemia occurred in patients treated with Rubraca, it is unclear if rucaparib increases the risk of these adverse reactions in this patient population, because these patients received prior treatment with platinum and other DNA damaging agents. Myelodysplastic syndrome and acute myeloid leukemia have also been observed in patients receiving Lynparza, the only other FDA-approved PARP inhibitor at the time this NDA was submitted. At this time, no additional nonclinical studies are warranted to support marketing of rucaparib for this indication, based on the proposed indication of advanced ovarian cancer.

Rucaparib was embryotoxic to rats in the absence of maternal toxicity at exposures lower than the human exposure at the recommended dose. In a dose range-finding embryo-fetal development study in which rats received oral doses of rucaparib during the period of organogenesis, post-implantation loss (100% early resorption) was observed in all animals at doses greater than or equal to 50 mg/kg/day, which resulted in maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$. Due to the results of the pilot study in rats, a pivotal GLP embryo-fetal development toxicity study in rats and a study in rabbits were not required to support an NDA submission for this proposed indication. Effective contraception for females of reproductive potential during treatment and for 6 months following the final dose of Rubraca was recommended since rucaparib was genotoxic and has a relatively short half-life. Additionally, because of the potential

for serious adverse reactions in breast-fed infants from rucaparib due to its mechanism of action and genotoxicity, it was recommended that prescribers advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose, based on the half-life of rucaparib of approximately 1.9 hours.

Fertility studies with rucaparib have not been conducted. In repeat-dose general toxicology studies, rucaparib administration had no effects on male and female reproductive organs at doses up to 100 mg/kg/day and 20 mg/kg/day in rats and dogs, respectively. These dose levels resulted in systemic exposures of approximately 0.3 and 0.09 times the human exposure (AUC_{0-24h}), respectively, at the recommended dose.

Since rucaparib demonstrated linear pharmacokinetics over a dose range from 240 mg to 840 mg twice-daily with time-independence and dose-proportionality, the human AUC_{0-12h} of 16900 h·ng/mL at the approved recommended dose of 600 mg orally twice-daily was doubled to estimate the AUC_{0-24h} of 33800 h·ng/mL in order to calculate the animal to human exposure ratios in sections 5.2, 8.1, and 13.1 of the label for Rubraca.

9.2. Referenced NDAs, BLAs, DMFs

None

9.3. Pharmacology

Primary pharmacology

In vitro, rucaparib inhibited enzymes in the PARP family. The IC_{50} values for several enzymes were below the plasma rucaparib unbound C_{max} of 1.79 μM observed in patients at 600 mg BID. Strongest inhibition was observed for PARP-1, PARP-2, and PARP-3, with IC_{50} values of 0.5, 0.8, and 28 nM, respectively (Study # Clovis_PARP_07302014).

Table 1. PARP Enzyme Inhibition by Rucaparib

Enzyme	IC_{50} (nM)
PARP-1	0.8
PARP-2	0.5
PARP-3	28
TNKS1 (PARP-5a)	796
TNKS2 (PARP-5b)	486
PARP-6	24000
PARP-7	5300
PARP-8	> 100000
PARP-10	1900
PARP-11	5800
PARP-12	2300
PARP-15	19800

In a panel of tumor cell lines, sensitivity to rucaparib correlated with homologous recombination (HR) deficiency as defined by decreased RAD51 staining (decreased foci formation) in human breast, ovarian, and prostate tumor cell lines. In ovarian tumor cell lines with HR deficiency, the EC_{50} for rucaparib ranged from 0.38 μM to 13 μM. Reintroduction of a wild-type BRCA1 allele into the ovarian cell line UWB1.289, which has low expression of a mutant form of BRCA1, restored HR function and increased the EC_{50} of rucaparib from 0.38 to 5.4 μM (Study # CO-338-TM001).

To further evaluate the contribution of genes involved in HR DNA repair to rucaparib sensitivity, siRNA was used to knock down 31 genes in select HR-proficient ovarian tumor cell lines (UWB1.289+BRCA1, SK-OV-3, OVCAR-3 and OAW-28). "Synthetic lethality" (defined as treatment with rucaparib resulting in an $EC_{50} \leq 30\%$ of non-transfected cell controls) was observed in cell lines with knockdown in BRCA1, BRCA2, RAD51, FACM, PALB2, ATR, or BARD1. All cell lines with BRCA1/2 knockdown exhibited synthetic lethality (except for UWB1.289+BRCA1). In the OVCAR-3 cell line, the EC_{50} values were 3.3, 3.0, 1.5, or 0.5 μM when the cell line was treated with non-targeting, PTEN, ATM, or BRCA1 siRNA, respectively (Study # CO-338-TM003).

Rucaparib-induced cell death of the UWB1.289 cell line was correlated with induction of apoptotic markers and decreased PAR formation. Specifically, rucaparib inhibited formation of PAR and induced DNA damage in a dose-dependent manner (IC_{50} = 2.8 nM and EC_{50} = 1.5 μM, respectively) after 24 hours of treatment. Increased annexin V staining was observed by day 3, but decreased viability was not observed until 5 days after treatment and was correlated with increased expression of caspase 3/7. A similar time course for decreased cell viability was observed for rucaparib-treated UWB1.289+BRCA1 cell line, but at significantly higher IC_{50} values ranging from 4827 to 8332 nM (Study # CO-338-TM005).

A literature reference was provided to support the hypothesis that the proposed mechanism of rucaparib may involve trapping of PARP-DNA complexes, similar to other PARP inhibitors olaparib and

BMN 673 (talazoparib) (Murai et al. Mol Cancer Ther 2014. 13:433-443). This process may interfere with DNA replication, which would require BRCA-dependent homologous recombination repair to resolve.

The anti-tumor effect of rucaparib was evaluated in various xenograft models of human breast and pancreatic cancers with either wild type or mutant *BRCA*. In a MDA-MB-436 (BRCA1 mutant) subcutaneous breast cancer xenograft model, antitumor activity resulting in statistically significant tumor growth inhibition (TGI) was observed by Day 17 at ≥ 150 mg/kg/dose QD or 150 mg/kg/dose BID (Study # 18-1201). In an orthotopic MDA-MB-436 breast cancer xenograft model in NOD/SCID mice, statistically significant TGI was observed on Day 28 at ≥ 2 mg/kg/dose BID, orally for 28 days (Study # E0157-U1508-CP-T001). Similar TGI was still observed on Day 39 when compared to Day 28. Anti-tumor activity was correlated with dose-dependent increases in rucaparib levels in the plasma and tumor and decreases in PAR levels in the tumor (statistically significant [$p < 0.05$] at ≥ 15 mg/kg/dose) (Study # CO-338-TM006).

Table 2. PK/PD Parameters Following Oral Dosing of Rucaparib in the MDA-MB-436 (BRCA1 Mutant) Xenograft Model

Dose (mg/kg/dose)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	PAR (ng/mL)	Rucaparib in tumor (ng/g)	Rucaparib in plasma (ng/mL)	TGI (%) on Day 28
0	N/A	N/A	1116	NR	0	N/A
2	26.3	NR	708	131	16	22
5	82	NR	766	134	27	30
15	173	718	617	340	68	58
50	2340	6870	151	1980	975	105
150	3550	20200	49	3970	1897	112

N/A = not applicable
NR = not reported

HBCx-17 is a ductal adenocarcinoma TNBC model with mutated TP53 and deleterious *BRCA2* mutation. In a subcutaneous HBCx-17 breast cancer patient-derived tumor xenograft model in female athymic (nu/nu) mice, administration of 50 or 150 mg/kg once-daily for 28 days (on Days 1-18 and 22-31) or 150 mg/kg twice-daily for 28 days (on Days 1-18 and 22-31) to tumor bearing mice resulted in statistically significant ($p < 0.001$) decreased tumor volume on Day 32.

HBCx-6 is a ductal adenocarcinoma TNBC model with mutated TP53 but without *BRCA1/2* mutations. In a subcutaneous HBCx-6 breast cancer patient-derived tumor xenograft model in female athymic (nu/nu) mice, administration of 50 or 150 mg/kg once-daily for 28 days or 300 twice-daily for 28 days to tumor bearing mice resulted in statistically significant ($p < 0.001$) decreased tumor volume on Day 28 when compared to control at ≥ 50 mg/kg/dose.

Secondary Pharmacology

The potential of rucaparib to inhibit off-target receptors, enzymes, and channels was evaluated in biochemical and cellular assays. In biochemical screening assays, rucaparib inhibited radioligand binding to the non-selective sigma (IC_{50} = 1.11 μM) and sodium channel site 2 (IC_{50} = 2.67 μM) binding sites. Follow-up studies suggest rucaparib may have moderate antagonistic activity towards the non-selective sigma receptor (Study # 1010522).

A kinase screen identified the following kinases with IC_{50} values lower than the plasma rucaparib unbound C_{max} of 1.79 μM observed in patients at 600 mg BID (Study # 20150224-CO-LR-KP-RV01 and 20150511-CO-LR-KP-RV02) .

Table 3. Inhibition of Kinases by Rucaparib

Enzyme	IC_{50} (μM)
CDK16/cyclin Y (PCTAIRE)	0.054
PASK	0.19
CDK17/cyclin Y (PCTK2)	0.22
PIM3	0.24
DYRK1/DYRK1A	0.42
DYRK1B	0.50
CDK18/cyclin Y (PCTK3)	0.60
MYO3b	0.76
MYO3A	0.83
PIM1	0.94
CDK6/cyclin D1	1.71

To evaluate the potential effect of rucaparib on PIM, PIM2, and PIM3 in cells, the Applicant conducted on in vitro assay using human embryonic kidney (HEK293) cells which were transiently transfected with expression plasmids encoding full length PIM1, PIM2, or PIM3, together with BAD, a substrate for PIM. Kinase activity was measured for the different PIM isoforms by measuring phosphorylation on BAD using an ELISA assay. Rucaparib did not have any significant inhibitory effects on PIM1, PIM2, or PIM3 (IC_{50} > 40 μM) (Study # 10781).

Safety Pharmacology

The effect of rucaparib on the human ether-a-go-go-related gene (hERG) channel current was evaluated using human embryonic kidney (HEK293) cell line transfected with human hERG cDNA and treated with 3, 10, 30, 100 μM rucaparib (Study # 150415-DMV). Rucaparib inhibited hERG potassium current with an IC_{50} value of 22.6 μM.

The effect of rucaparib on blood pressure, heart rate, and cardiac rhythm parameters was evaluated in a GLP safety pharmacology study in male telemetered beagle dogs (Study # 2908). In the study, animals were administered a single 30-minute intravenous infusion of control (mannitol), or 5 or 15 mg/kg rucaparib using a 3-way cross-over design. No adverse findings on cardiovascular parameters were observed (NOAEL = 15 mg/kg; C_{max} = 2542 ng/mL; $AUC_{0\text{-}24h}$ = 6781 ng·h/mL).

The effect of rucaparib on nervous system function was evaluated in a GLP study in male Sprague-Dawley rats (Study # 2913). In the study, animals were administered control (mannitol), or 15, 50 or 75 mg/kg rucaparib by a single 5-minute IV infusion. At approximately 30 minutes postdose, animals were evaluated for neuronal function and reflex/activity monitoring. A dose of 75 mg/kg IV was not tolerated as animals exhibited severe clinical signs (i.e., dyspnea, hypoactivity, prostrate, ataxia, soft feces) and death. Decreased motor activity (i.e., decreased total distance traveled and number of vertical movements) was observed at 50 mg/kg. No adverse findings were observed at 15 mg/kg (C_{max} = 3468 ng/mL).

9.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Pharmacokinetics of AG014447 in male cynomolgus monkeys, male dogs and male Sprague-Dawley rats (Study # AG014699-PDM-006)</td><td>Mean PK parameters in male monkeys, dogs and rats dosed with 15 mg/kg AG014698 (glucoronate salt of AG014447) IV:
<table>
<tr><th></th><th>Monkey (n = 3)</th><th>Dog (n = 3)</th><th>Rat (n = 3)</th></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (μg·h/mL)</td><td>7.4</td><td>4.1</td><td>5.7</td></tr>
<tr><td>CL (mL/min/kg)</td><td>33.8</td><td>61.8</td><td>45.3</td></tr>
<tr><td>Vd (L/kg)</td><td>7.2</td><td>15.2</td><td>6.5</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>5.2</td><td>4.5</td><td>3.5</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Pharmacokinetics of rucaparib following single oral administration of rucaparib camsylate in non-tumor bearing NOD/SCID mice (Study # E0157-U1509-CP-T001)</td><td>Plasma PK parameters of rucaparib following a single oral dose to female NOD/SCID mice:
<table>
<tr><th rowspan="2">Parameter</th><th colspan="5">Groups (mg/kg)</th></tr>
<tr><th>2</th><th>5</th><th>15</th><th>50</th><th>150</th></tr>
<tr><td>T_{max} (h)</td><td>1.00</td><td>1.00</td><td>2.00</td><td>2.00</td><td>2.00</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>26.3</td><td>82.0</td><td>173</td><td>2340</td><td>3550</td></tr>
<tr><td>AUC_{0-t} (ng·h/mL)</td><td>115</td><td>221</td><td>682</td><td>6850</td><td>20000</td></tr>
<tr><td>AUC_{0-inf} (ng·h/mL)</td><td>NR</td><td>NR</td><td>718</td><td>6870</td><td>20200</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>NR</td><td>NR</td><td>2.93</td><td>1.23</td><td>1.48</td></tr>
<tr><td>Cl/F (mL/h/kg)</td><td>NR</td><td>NR</td><td>20900</td><td>7280</td><td>7420</td></tr>
<tr><td>Vz/F (mL/kg)</td><td>NR</td><td>NR</td><td>88300</td><td>12900</td><td>15800</td></tr>
</table>
N/A = not applicable
NR = not reportable</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Excretion mass balance and tissue distribution by quantitative whole body autoradiography in rats following a single oral dose of [^{14}C]rucaparib camsylate and an estimate of human radiation dosimetry (Study # 454N-1501)</td><td>- The primary route of elimination of radioactivity after an oral administration of [^{14}C]rucaparib in rats was through the feces (93% to 94.7% of the administered dose).
- [^{14}C]Rucaparib partitioned approximately equally into plasma and blood in male rats but partitioned more in the blood than plasma in female rats.
- C_{max} in most tissues was observed 6 h and 4 h post-dose in SD and LE rats, respectively.
- The highest tissue concentrations in male SD rats were observed in the cecum, kidney medulla, adrenal gland medulla, stomach, liver, and small intestine. Data suggest that there is minimal crossing of the blood-brain (< 20% of blood levels) following oral administration in rats. Higher and more persistent tissue distribution in pigmented tissues (e.g., eye uvea and pigmented skin) was observed.</td></tr>
<tr><td>Determination of plasma protein binding properties and RBC-to-plasma concentration ratio for AG-014447 in the mouse, rat, dog and human (Study # AG014699-PDM-012)</td><td>Mean plasma protein binding of AG-014447 (%bound):
Mouse: 61.9%
Rat: 56.4%
Dog: 66.8%
Human: 70.2%

In vitro mean RBC-to-plasma ratio for AG-014447:
Mouse: 2.26 – 5.85</td></tr>
</table>

Type of Study	Major Findings
	Rat: 4.37 Dog: 5.21 Human: 1.83
Metabolism	
In vitro metabolism of AG-014447 in human and animal liver microsomes and hepatocytes (Study # AG014699-PDM-009)	In vitro, similar metabolites were observed from rat, dog, and human hepatocytes.
Excretion	
Absorption, excretion/mass balance, and radiokinetics of [^{14}C]rucaparib camsylate in naïve male and female beagle dogs following a single oral administration (Study # 11640)	- There were no apparent sex-dependent differences. - Following a single oral administration to fed dogs, mean recovery of the radioactive dose through 168 h after dosing was approximately 89%. The majority of total radioactivity recovery in excreta (79%) occurred in the first 48 hours post-dose. - Fecal excretion was the major route of elimination, accounting for ≥ 79% of the total dose. - T_{max} = 2.5 h – 2.67 h - $T_{1/2}$ = 4 h – 4.62 h - Mean blood to plasma ratios = 1.35 – 1.62
TK data from general toxicology studies 13-Week oral study in rats (Study # 8258077) 13-Week oral study in dogs (Study # 8258073)	 <u>13-Week rat study</u> $T_{1/2}$: 2.12 – 3.08 h on Day 1 and 3.34 – 3.65 h on Day 92 Sex differences: No Accumulation: No Dose proportionality: Approximately dose-proportional between 10 and 40 mg/kg/day and less than dose-proportional between 10 and 100 mg/kg/day. <u>13-Week dog study</u> $T_{1/2}$: 3.22 – 4.35 h on Day 1 and 1.86 – 3.58 h on Day 91 Sex differences: No Accumulation: No Dose proportionality: Approximately dose-proportional on Day 1 and greater than dose proportional on Day 91.
TK data from reproductive toxicology studies Dose range-finding embryo-fetal	 <u>Maternal</u>

Type of Study	Major Findings
development study in rats (Study # 20048401)	$T_{1/2}$: 2.42 – 3.92 h Accumulation: Yes; at 1000 mg/kg/day Dose proportionality: Yes AUC_{0-24} (GD 17; mean; ng·h/mL): 50 mg/kg/day: 922 150 mg/kg/day: 3840 500 mg/kg/day: 7320 1000 mg/kg/day: 12900

9.5. Toxicology

9.5.1. General Toxicology

Study title/ number: 13-Week oral gavage toxicity and toxicokinetic study with rucaparib in rats with a 28-day recovery phase/ 8258077

Key Study Findings

- There were no test article-related mortalities.
- Target organs included the bone marrow (hypocellularity) and lymphoid organs (lymph node and GALT/Peyer's Patch; decreased lymphocytes).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 40, 100 mg/kg/day, once-daily
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose (400 cps) in reverse osmosis water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	15/sex/group (toxicity) and 3-6/sex/group (toxicokinetic)
Age:	10 to 11 weeks old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Table 4. Observations and Results in Rat Toxicology Study (Changes from Control)

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>No test article-related mortality was observed.</td></tr>
<tr><td>Clinical Signs</td><td>No test article-related clinical signs were observed.</td></tr>
<tr><td>Body Weights</td><td>End-of-dosing (body weight/body weight gain):
MD: -7.99%/-16.8% (males) and -8.9%/-19.1% (females)
HD: -8.8%/-39.2% (males) and -6.3%/-29.1% (females)</td></tr>
<tr><td>Food Consumption</td><td>Statistically significant and reversible decreases (< 22% compared to control) in food consumption were observed in MD and HD animals during the dosing phase.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Functional Observational Battery</td><td>Unremarkable</td></tr>
<tr><td>Motor Activity</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Decreased RBC count at MD (≤ -10%) and HD (≤ -19%).
Decreased hemoglobin (≤ -1.2%), hematocrit (≤ -4%), reticulocyte count (≤ -23%), WBC count (≤ -30%), absolute lymphocyte count (≤ -35%) at HD.
All hematologic changes were reversible.</td></tr>
<tr><td>Clinical Chemistry</td><td>Decreased total protein (≤ -7%), globulin (≤ -12%), albumin (-5%) at MD and HD.
Decreased cholesterol (-22%) at HD.
Increased albumin:globulin ratio (≤ 19%) at MD and HD.
All clinical chemistry changes were reversible except for decreased globulin.</td></tr>
<tr><td>Urinalysis</td><td>Reversible higher urine volume (140%) at HD and lower urine specific gravity (≤ -1.2%) at MD and HD.</td></tr>
<tr><td>Gross Pathology</td><td>Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>Unremarkable</td></tr>
<tr><td>Histopathology

Adequate battery: Yes</td><td>Reversible histopathologic findings were observed in the bone marrow, lymph node, and GALT/Peyer’s Patch.
<table>
<tr><th></th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th></th><th>C</th><th>LD</th><th>MD</th><th>HD</th><th>C</th><th>LD</th><th>MD</th><th>HD</th></tr>
<tr><td>Bone marrow, femur
Hypocellular
Minimal
Slight</td><td></td><td></td><td></td><td>

2
4</td><td></td><td></td><td></td><td>

1</td></tr>
<tr><td>Bone marrow, sternum
Hypocellular
Minimal</td><td></td><td></td><td></td><td>

3</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lymph node, mandibular</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

	Lymphocytes, decreased Minimal			6	9			6	7
	GALT/Peyer's Patch Lymphocytes, decreased Minimal			4	4			5	6
Stage-Aware Spermatogenesis Evaluation	No remarkable changes in organ weights or macroscopic and microscopic findings were observed in the testes and epididymis. Normal progression of the stages of the spermatogenic cycle and expected proportions of the various stages occurring during normal spermatogenesis were observed in the testes (stage aware) and left epididymis.								
Male Reproductive Assessment	No test article-related effects on mean sperm total count, density, motility, or morphology were observed.								
Toxicokinetics	See ADME/PK section 9.4 above								

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

Study title/ number: A 13-week repeat-dose oral capsule toxicity and toxicokinetic study with rucaparib in beagle dogs with a 4 week recovery/ 8258073

Key Study Findings

- One HD male animal was sacrificed in moribund condition on Day 18. Major findings in this animal included decreased red cell and white cell counts which correlated with histopathological findings of bone marrow hypocellularity and lymphoid depletion. Additional histopathological findings included hemorrhage and degeneration/necrosis in the adrenal cortex and hemorrhage in the gastrointestinal tract.
- The target organ of toxicity in animals that survived until their scheduled necropsy was the bone marrow (erythroid atrophy).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 15/10, 40/30/20 mg/kg/day, once-daily
Route of administration: Oral
Formulation/Vehicle: Empty gelatin capsules
Species/Strain: Dog/beagle
Number/Sex/Group: 5
Age: 9 Months old

Satellite groups/ unique design: Animals in the HD group were on a dosing holiday beginning on Day 16 of the dosing phase. Dosing resumed for HD animals on Day 21 at 30 mg/kg/day. Beginning on Day 23, HD animals were on a second dose holiday. Dosing for HD animals resumed on Day 27 at 20 mg/kg/day. The dose level for MD animals was reduced to 10 mg/kg/day beginning on Day 26.

Deviation from study protocol affecting interpretation of results: No

Table 5. Observations and Results in Dog Toxicology Study (Changes from Control)

Parameters	**Major findings**
Mortality	LD female (H08305): sacrificed on Day 42 due to dosing error (capsule found in the intra-tracheal region past the epiglottis at necropsy) HD male (H08299): sacrificed in moribund condition on Day 18 - Clinical signs: hypoactive, thin, pale gums, red/liquid/mucoid feces, lethargic, fever, laterally recumbent. - Clinical pathology: decreased reticulocyte, platelet and white blood cell counts, and albumin-to-globulin ratio. Increased fibrinogen, globulin, serum bilirubin, and alkaline phosphatase. - Histopathology: moderate bone marrow hypocellularity; minimal to moderate lymphoid depletion in GALT/Peyer's patch, lymph nodes, thymus cortex, and splenic white pulp; minimal hemorrhage and degeneration/necrosis in the adrenal cortex; and minimal to slight hemorrhage in the cecum, colon, ileum, and rectum.
Clinical Signs	Non-formed feces at ≥ LD Thin at ≥ MD (reversible)
Body Weights	Absolute/percentage change in mean body weight: Males MD: Days 1 to 25: -40 g/-0.4% HD: Days 1 to 15: -780 g/-8.0% Days 1 to 25: -425 g/-4.2% Females HD: Days 1 to 15: -220 g/-3.4% Days 1 to 25: -160 g/-2.5% Percentage change in mean body weight gain from control (Days 25 – 90; males/females): LD: 6.5%/-60.2%

<table>
<tr><td></td><td>MD: -12.9%/27.3%
HD: -11.3%/4.5%</td></tr>
<tr><td>Food Consumption</td><td>HD: -19.3% to -42.6% until Day 11 (all animals were place on canned food supplementation starting from Day 7)</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Physical Examinations, Respiration Rates, Vital Signs, and Blood Pressure Measurements</td><td>Unremarkable</td></tr>
<tr><td>ECG</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Decreased RBC count (≤ -21%), hemoglobin (≤ -18%), and hematocrit (≤ -15%) at HD.
Increased MCV (≤ 8%) at LD, MD, and HD in males and HD in females.
All hematologic changes were reversible.</td></tr>
<tr><td>Clinical Chemistry</td><td>Unremarkable</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>Discolored ileum in one HD female at the recovery necropsy (correlating with histopathological finding of minimal congestion in the ileum)</td></tr>
<tr><td>Organ Weights</td><td>Unremarkable</td></tr>
<tr><td>Histopathology

Adequate battery: Yes</td><td>Reversible histopathologic findings of minimal erythroid atrophy were noted in the femur and sternum bone marrow.

<table>
<tr><th></th><th colspan="4">Males</th><th colspan="4">Females</th></tr>
<tr><th></th><th>C</th><th>LD</th><th>MD</th><th>HD</th><th>C</th><th>LD</th><th>MD</th><th>HD</th></tr>
<tr><td>Bone marrow, femur
Atrophy, erythroid
Minimal</td><td></td><td></td><td>2</td><td></td><td></td><td></td><td></td><td>2</td></tr>
<tr><td>Bone marrow, sternum
Atrophy, erythroid
Minimal</td><td></td><td></td><td>2</td><td></td><td></td><td></td><td></td><td>2</td></tr>
</table>

The following findings were observed in one recovery HD female animal: minimal congestion in the colon and ileum, slight GALT hyperplasia with dilated lacteals in the ileum, slight crypt hyperplasia with villous blunting in the ileum, and slight neutrophil infiltrate in the ileum.</td></tr>
<tr><td>Toxicokinetics</td><td>See ADME/PK section 9.4 above</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters.

General toxicology; additional studies

Study title/ number: A 28-day repeat-dose oral gavage toxicity and toxicokinetic study of rucaparib with a 28-day recovery phase on Sprague Dawley rats/ 8258076

In this GLP-compliant study, vehicle control [0.5% (w/v) methylcellulose in reverse osmosis water] or 50, 150, or 500 mg/kg/day rucaparib was administered orally, once-daily for 28 days to Crl:CD(SD) rats. Three mortalities occurred in the study (one female at 150 mg/kg/day; one male and one female at 500 mg/kg/day). No significant findings were observed in the animal at 150 mg/kg/day, while anemia was most likely the cause of death for the animals at 500 mg/kg/day. Test article-related clinical signs included reversible thinning coat and pale eyes at ≥ 150 mg/kg. Statistically significant decreased body weight was observed at 500 mg/kg/day in male animals and it persisted through the recovery period. Decreased red cell mass and white blood cell count was observed at ≥ 150 mg/kg/day and correlated with reversible histopathological findings of atrophy in the bone marrow and spleen and decreased lymphocytes in multiple lymphoid tissues (e.g., thymus, GALT, lymph nodes) at ≥ 150 mg/kg/day. Additionally, reversible subacute inflammation in the cecal lamina propria accompanied by degeneration and necrosis of cryptal or luminal epithelium was observed at 500 mg/kg/day.

Study title/ number: 1-Month oral toxicity study of PF-01367338 in dogs with a 1-month recovery/ 09GR456

In this GLP-compliant study, 0 (empty gelatin capsules), 5, 20, or 75 mg/kg/day rucaparib in gelatin capsules was administered orally, once-daily for 30 days to beagle dogs. There were no mortalities considered to be related to rucaparib. One female animal at 75 mg/kg was euthanized before the scheduled necropsy and was noted with a necropsy finding of non-reducible intussusception in the mid-jejunum. The finding was considered to be incidental and not related to rucaparib. Abnormal stools were observed at all dose levels and decreased activity and decreased food consumption were observed at 75 mg/kg. Rucaparib-related changes in clinical pathology parameters included decreases in red blood cell and white blood cell counts at ≥ 20 mg/kg. Histopathological findings included bone marrow hypocellularity and decreased lymphocyte cellularity in GALT, thymus, and lymph nodes (mesenteric and popliteal). Ulceration of renal pelvic epithelium, ulceration in cecum, splenic lymphoid necrosis with fibrin exudation, and hepatic glycogen depletion were observed in one animal at 75 mg/kg. All findings were not observed following the recovery period.

9.5.2. **Genetic Toxicology**

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Microbial reverse mutation assays / 02-2371-01

Key Study Findings:

- In the in vitro bacterial reverse mutation assay with the plate incorporation method, rucaparib produced positive mutagenic response at concentrations ranging from 0.50 to 1.0 mg/plate in the *Salmonella* strain TA 98 without metabolic activation under the conditions tested.

GLP compliance:	Yes
Test system:	Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 and Escherichia coli strain WP2 uvrA pKM101; up to 5.0 mg/plate +/- S9
Study is valid:	Yes

Table 6. Bacterial Reverse Mutation Assay (Preliminary Assay Without S9 – Test No. 1B)

Test article	Concentration/plate	# of revertant colonies per plate ± SD
DMSO (mL)	0.10	25 ± 1
2-Nitrofluorene (mg)	0.005	1280 ± 148
Rucaparib (mg)	0.01	26 ± 1
Rucaparib (mg)	0.05	31 ± 6
Rucaparib (mg)	0.2	34 ± 11
Rucaparib (mg)	1.0	54 ± 4
Rucaparib (mg)	5	TOX

Historical background value for the TA98 strain without S9 (1997-2002): Mean = 24 ± 7 (range = 8 – 49).

Table 7. Bacterial Reverse Mutation Assay (Confirmatory Definitive Assay Without S9 – Test No. 4)

Test article	Concentration/plate	# of revertant colonies per plate ± SD
DMSO (mL)	0.10	26 ± 8
2-Nitrofluorene (mg)	0.005	1450 ± 36
Rucaparib (mg)	0.5	52 ± 5
Rucaparib (mg)	0.75	45 ± 5
Rucaparib (mg)	1.0	42 ± 10
Rucaparib (mg)	1.25	37 ± 9*
Rucaparib (mg)	1.5	34 ± 8*

Historical background value for the TA98 strain without S9 (1997-2002): Mean = 24 ± 7 (range = 8 – 49).

* Cytotoxicity (decreased lawn density when compared to control) was observed at ≥ 1.25 mg/plate.

In Vitro Assays in Mammalian Cells

Study title/ number: In vitro cytogenetic assays / 02-2371-02

Key Study Findings:

- Rucaparib induced increases in structural chromosome aberrations in human lymphocyte cultures in vitro, both in the presence and absence of metabolic activation under the conditions tested.

GLP compliance:	Yes
Test system:	Human peripheral lymphocyte; up to 5 mg/mL; +/- S9
Study is valid:	Yes

Table 8. In Vitro Chromosomal Aberration Assay

Treatment	Mean (%) Mitotic Suppression	Mean (%) Abnormal Cells	Mean (%) Polyploid Cells
Without metabolic activation (-S9) – 3 hr incubation			
DMSO, 1%	0	2	0.2
Rucaparib, 10.8 μg/mL	17	4*	0.1
Rucaparib, 15.4 μg/mL	30	4*	0.2
Rucaparib, 16.8 μg/mL	51	8.5*	0.2
Mitomycin-C, 0.4 μg/ml	25	26*	ND
With metabolic activation (+S9) – 3 hr incubation			
DMSO, 1%	0	0.5	0.2
Rucaparib, 20.5 μg/mL	28	3	0.4
Rucaparib, 25.6 μg/mL	47	6*	0.7
Rucaparib, 32.0 μg/mL	65	5.5*	0.2
Cyclophosphamide, 10.0 μg/mL	60	30**	ND
Without metabolic activation (-S9) – 24 hr incubation			
DMSO, 1%	0	1.5	0.1
Rucaparib, 2.41 μg/mL	10	5.0*	0.1
Rucaparib, 3.76 μg/mL	31	13**	0.1
Rucaparib, 5.88 μg/mL	55	25**	0.1
Mitomycin-C, 0.05 μg/mL	20	24**	ND

* $p < 0.05$ (1-tailed Fisher's Exact test compared to control values)

** $p < 0.001$ (1-tailed Fisher's Exact test compared to control values)

ND = Not determined

(b) (4)

Not conducted per prior agreement with the Division based on positive in vitro findings and the mechanism of action of rucaparib.

9.5.3. **Carcinogenicity**

Not conducted and not required to support this NDA submission for a therapeutic intended to treat patients with advanced cancer.

9.5.4. **Reproductive and Developmental Toxicology**

Fertility and Early Embryonic Development

Not conducted and not required to support this NDA submission for a therapeutic intended to treat patients with advanced cancer.

Embryo-Fetal Development

Study title/ number: "A dose range-finding embryo-fetal development study of rucaparib by oral gavage in rats." Study No. 20048401

Key Study Findings

- Complete litter loss (100% early resorption) was observed in all dose groups administered rucaparib.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Non-GLP

Methods

Dose and frequency of dosing:	0, 50, 150, 500, 1000 mg/kg/day (10 mL/kg), once-daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) methylcellulose (400 cps) in R.O. deionized water
Species/Strain:	Rats/Crl:CD(SD) Sprague-Dawley
Number/Sex/Group:	8 females/group
Satellite groups:	5 females/group
Study design:	Gestating female rats of approximately 56 to 70 days of age were administered 0, 50, 150, 500, or 1000

	mg/kg/day rucaparib by oral gavage, once-daily on GD 7 through 17. Animals were euthanized on GD 21.
Deviation from study protocol affecting interpretation of results:	No

Table 9. Observations and Results of Rat Embryo-Fetal Toxicology Study

Parameters	**Major findings**
Mortality	None
Clinical Signs	1000 mg/kg/day: suspected dehydration (8/8), hunched posture (1/8), scab on the skin (1/8), thin fur (1/8), abnormal sounds during breathing (1/8), liquid discharge from the vagina (3/8), pale feces (8/8), and purple skin (1/8). 500 mg/kg/day: suspected dehydration (2/8) and pale feces (7/8).
Body Weights	500 mg/kg/day: -16%/-83% (absolute/gain) and -32%/-101% (absolute/gain) compared to control on GD 17 and GD 21, respectively. 1000 mg/kg/day: -19%/-96% (absolute/gain) and -33%/-86% (absolute/gain) compared to control on GD 17 and GD 21, respectively.
Food Consumption	500 mg/kg/day: -24% and -25% compared to control during GD 7 – 18 and GD 7 – 21, respectively. 1000 mg/kg/day: -33% and -32% compared to control during GD 7 – 18 and GD 7 – 21, respectively.
Necropsy findings Cesarean Section Data *[Implantation Sites, Pre- and Post-Implantation Loss, etc.]*	Pregnancy occurred in all rats. Complete litter loss (100% early resorption) was observed in all rucaparib-treated groups.
Necropsy findings Offspring *[malformations, variations, etc]*	Not conducted due to 100% early resorption in all treated groups.
Toxicokinetics	See ADME/PK section 9.4 above

Prenatal and Postnatal Development

Not conducted and not required to support this NDA submission for a therapeutic intended to treat patients with advanced cancer.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAW-JYH CHIU
11/22/2016

TODD R PALMBY
11/22/2016

JOHN K LEIGHTON
11/23/2016

10. Clinical Pharmacology

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10.1. Executive Summary

Rubraca (rucaparib), a new molecular entity, is a small molecule poly (ADP-ribose) polymerase (PARP) inhibitor. Based on two Phase 2 trials (CO-338-010 and CO-338-017), the applicant seeks an accelerated approval of rucaparib for the treatment of advanced ovarian cancer in patients with deleterious BRCA mutations (germline and somatic), and who have been treated with two or more chemotherapies.

Clinical pharmacology review focused on appropriateness of the proposed dose, food effect, potential drug interactions, and recommended dose adjustment for patients with hepatic or renal impairment. The key findings are:

- The proposed dosing regimen of 600 mg rucaparib twice daily with or without food is acceptable.
- It is acceptable to administer rucaparib with or without food, given the magnitude of food effect (a 38% increase in AUC) and a large PK variability (54% CV for steady-state AUC).
- Though CYP2D6, CYP1A2 and CYP3A4 are the cytochrome P450 (CYP) enzymes involved in the metabolism of rucaparib *in vitro*, the contribution of metabolism to the total elimination of rucaparib is unknown. Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib did not differ significantly across CYP2D6 or CYP1A2 genotype-predicted phenotypes, and drug-drug interaction potential of rucaparib as a CYP1A2 or CYP2D6 substrate is low. A (b) (4) drug-drug interaction (DDI) trial (CO-338-044) with probes of CYP1A2, CYP2C19, CYP2C9, CYP3A, and P-gp is ongoing.
- No dose adjustment is recommended for patients with mild hepatic impairment or mild to moderate renal impairment. No dose recommendation can be made for patients with moderate to severe hepatic impairment or severe renal impairment due to a lack of data.

10.1.1. Recommendations

The Office of Clinical Pharmacology concluded that the submission of NDA 209115 for rucaparib is approvable from a clinical pharmacology perspective, provided that the applicant and the agency come to a mutual agreement regarding the labeling language and the post-marketing requirements and commitment.

The key review issues with specific recommendations/comments are summarized below:

Key Review Issues	Recommendations and Comments
Dose selection & food effect	The proposed dose of 600 mg rucaparib twice daily (BID) is acceptable. It is acceptable to administer rucaparib with or without food, given the magnitude of food effect (a 38% increase in AUC) and a large PK variability (54% CV for steady-state AUC). Labeling recommendation: The recommended dose of rucaparib is 600 mg (two

Key Review Issues	Recommendations and Comments
	300 mg tablet) taken orally twice daily with or without food.
DDI potential	Though CYP2D6, CYP1A2 and CYP3A4 are the cytochrome P450 (CYP) enzymes involved in the metabolism of rucaparib *in vitro*, the contribution of metabolism to the total elimination of rucaparib is unknown. Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib did not differ significantly across CYP2D6 or CYP1A2 genotype-predicted phenotypes, and drug-drug interaction potential of rucaparib as a CYP1A2 or CYP2D6 substrate is low. The ongoing mass balance trial CO-338-045 will provide more information regarding the metabolism of rucaparib in humans. *In vitro*, rucaparib was a substrate of transporters, P-gp and BCRP; a reversible inhibitor of CYP1A2, CYP2C19, CYP2C9, and CYP3A; and an inducer of CYP1A2. Furthermore, rucaparib was a potent inhibitor of MATE 1 and MATE2-K, and a moderate inhibitor of OCT1. A (b) (4) DDI trial (CO-338-044) with probes of CYP1A2, CYP2C19, CYP2C9, CYP3A, and P-gp is ongoing. PMR: A PMR will be issued to request submission of the final study report of ongoing (b) (4) DDI trial (CO-338-044). Labeling recommendation: Describe the available information for potential DDI.
Dose adjustment in patients with renal impairment	Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild to moderate renal impairment. No data were available in patients with severe renal impairment. Labeling recommendation: No dose adjustment is recommended for patients with mild to moderate renal impairment (creatinine clearance [CrCL] between 30 mL/min and 89 mL/min, as estimated by the Cockcroft-Gault method). No data were available in patients with severe renal impairment (CrCL less than 30 mL/min, as estimated by the Cockcroft-Gault method).
Dose adjustment in patients with hepatic impairment	Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild hepatic impairment. Only limited data (N=2) were available in patients with moderate hepatic impairment. No data were available in patients with severe hepatic impairment. PMR: A PMR will be issued to determine the appropriate starting dose in patients with moderate hepatic impairment. Labeling recommendation: No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation of appropriate starting dose can be made for patients with moderate hepatic impairment (total bilirubin between

Key Review Issues	Recommendations and Comments
	1.5 times and 3 times ULN) due to limited data (N=2). No data were available in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN).

10.1.2. Post-Marketing Requirement (PMR) and Commitment (PMC)

The following issues should be addressed as PMRs:

1. Submit the final study report of ongoing drug-drug interaction trial CO-338-044.
2. Determine the appropriate starting dose in patients with moderate hepatic impairment.

The following issue should be addressed as a PMC:

1. Submit the final study report of ongoing mass balance trial CO-338-045.

10.2. Summary of Clinical Pharmacology Assessment

Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. All pharmacokinetics of rucaparib were characterized in patients with cancer. Rucaparib demonstrated linear pharmacokinetics over a dose range from 240 to 840 mg twice daily with time-independence and dose-proportionality. The mean steady-state rucaparib C_{max} was 1940 ng/mL (54% coefficient of variation [CV]) and AUC_{0-12h} was 16900 h·ng/mL (54% CV) at the approved recommended dose. The accumulation was 3.5 to 6.2 fold. The median terminal half-life ($T_{1/2}$) was 17 hours.

10.2.1. Pharmacology and Clinical Pharmacokinetics

The following is a summary of the clinical pharmacokinetics (PK) of rucaparib.

Absorption: The median T_{max} was 1.9 hours at the approved recommended dose. The mean absolute bioavailability of rucaparib immediate-release tablet was 36% with a range from 30% to 45%. Following a high-fat meal, C_{max} was increased by 20% and AUC_{0-24h} was increased by 38%, and T_{max} was delayed by 2.5 hours, as compared to dosing under fasted conditions.

Distribution: Rucaparib had a steady-state volume of distribution of 113 L to 262 L following a single intravenous dose of 12 mg to 40 mg. *In vitro*, the protein binding of rucaparib was 70% in human plasma at therapeutic concentrations. *In vitro*, rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.8.

Elimination: The mean terminal $T_{1/2}$ of rucaparib ranged from 17 to 19 hours, following a single oral dose of 600 mg rucaparib. The apparent clearance ranged from 15.3 to 79.2 L/hour, following

continuous 600 mg rucaparib orally twice daily. The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous rucaparib dose ranging from 12 mg to 40 mg.

Metabolism: *In vitro*, rucaparib had a low metabolic turnover rate in human liver microsomes, and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4.

10.2.2. General Dosing and Therapeutic Individualization

General Dosing

Based on PK and exposure-response analyses for safety and efficacy of rucaparib, the proposed dosing regimen of 600 mg rucaparib twice daily with or without food is acceptable.

Therapeutic Individualization

Hepatic impairment: Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). There were limited data (N=2) in patients with moderate hepatic impairment (total bilirubin between 1.5 times and 3 times ULN). No data were available in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN). A PMR will be issued to determine the appropriate starting dose in patients with moderate hepatic impairment.

Renal impairment: Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild to moderate renal impairment (CrCL between 30 mL/min and 89 mL/min, as estimated by the Cockcroft-Gault method). No data were available in patients with severe renal impairment (CrCL less than 30 mL/min, as estimated by the Cockcroft-Gault method).

CYP enzyme polymorphism: Based on population PK analyses, for patients taking 600 mg rucaparib twice daily, there appeared to be no significant difference in steady-state exposure of rucaparib among CYP2D6 phenotypes (poor metabolizers, N=9; intermediate metabolizers, N=69; normal metabolizers, N=75; ultra-rapid metabolizers, N=4) or between CYP1A2 normal metabolizers (N=28) and hyper-inducers (N=133).

Food effect: It is acceptable to administer rucaparib with or without food, given the mild magnitude of food effect (a 38% increase in AUC) and a large PK variability (54% CV for steady-state AUC).

BRCA mutation type: Confirmed ORR (by investigator) was similar regardless of BRCA mutation type (germline vs. somatic) and BRCA gene mutation (*BRCA1* vs *BRCA2;* see Appendix 4.5).

Outstanding Issues

Two PMRs will be issued:

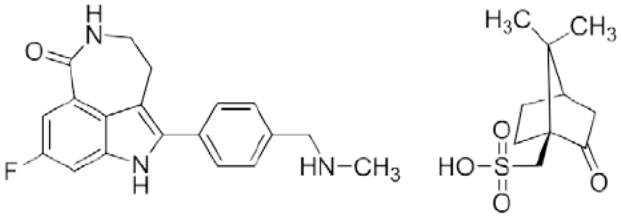
1. Submit the final study report of ongoing drug-drug interaction trial CO-338-044.

2. Determine the appropriate starting dose in patients with moderate hepatic impairment.

Furthermore, a PMC will be issued to request submission of the final study report of ongoing mass balance trial CO-338-045.

10.3. Comprehensive Clinical Pharmacology Review

10.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Chemical structure	
Molecular weight (g/mol)	555.67
Aqueous solubility	1.4 mg/mL in water at 25°C; 1.7 mg /mL in water at 37°C; pH-independent between pH 3 and 7; lower solubility at pH 1 and 2
Mechanism of action	Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1 (IC_{50}=0.8 nM), PARP-2 (IC_{50}=0.8 nM), and PARP-3 (IC_{50}=28 nM), which play a role in DNA repair.
Active moieties	Rucaparib was shown to be the only active moiety.
QT/QTc prolongation	The effects of rucaparib on QTc prolongation were evaluated in 56 patients from the part 1 of study CO-338-010. A significant relationship between QTcF increase from baseline and rucaparib exposure was observed. The mean QTcF increase from baseline (90% confidence interval [CI]) in population PK estimated 95% percentile C_{max} (3019 ng/mL) at steady state of 600 mg rucaparib twice daily was 14.9 msec (11.1-18.7 msec).
Pharmacokinetic Characteristics	
Bioanalysis	Only rucaparib was measured using validated HPLC/MS/MS methods. A summary of the method validation reports is included as an appendix.
Exposure at steady state following	At dose level of 600 mg twice daily, the mean (± SD) steady-

the therapeutic dosing regimen	state C_{max} and AUC_{0-12} were 1940 (± 1050) ng/mL and 16900 (± 9140) ng·hr/mL.
Variability	CV% for C_{max} was 54% and for AUC_{0-12} was 54%.
Minimal effective dose or exposure	Based on meta-analyses of the available Phase 1/2 PK, safety, and efficacy data of olaparib and niraparib, the minimal effective concentration of rucaparib was about 650 ng/mL.
Maximal tolerated dose or exposure	Maximal tolerated dose was not reached with doses evaluated up to 840 mg.
Dose proportionality	Rucaparib demonstrated linear PK over an oral QD dose range from 40 to 500 mg and an oral BID dose range from 240 to 840 mg.
Time-dependent/independent PK	PK of rucaparib is time-independent.
Accumulation	Accumulation was 3.5 to 6.2 fold.
Absorption	
Bioavailability	The mean absolute bioavailability of rucaparib immediate-release tablet was 36% with a range from 30% to 45%.
T_{max}	The median T_{max} was 1.9 hours at the proposed recommended dose.
Food effect	Following a high-fat meal, C_{max} was increased by 20% and AUC_{0-24} was increased by 38%, and T_{max} was delayed by 2.5 hours, as compared to dosing under fasted conditions.
Distribution	
Volume of distribution	Rucaparib had a steady-state volume of distribution of 113 L to 262 L following a single intravenous dose of 12 mg to 40 mg.
Plasma protein binding	*In vitro*, the protein binding of rucaparib was 70% in human plasma at therapeutic concentrations.
Blood to plasma ratio	*In vitro*, rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.8.
Elimination	
Terminal half-life ($T_{1/2}$)	The mean terminal $T_{1/2}$ of rucaparib was about 17 to 19 hours,

	following a single oral dose of 600 mg rucaparib.
Clearance	The apparent clearance ranged from 15.3 to 79.2 L/hour, following continuous 600 mg rucaparib orally twice daily. The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous rucaparib dose ranging from 12 mg to 40 mg.
Metabolism	
Primary metabolic pathways	*In vitro*, rucaparib had a low metabolic turnover rate in human liver microsomes, and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Rucaparib, M324, and M338 were the major circulating drug-related identities in the plasma from three patients, accounting for about 43.5% to 55.1%, 16.8% to 20.0%, and 12.8% to 24.9% of the total rucaparib-related peak area, respectively. M324 was a carboxylic acid and M338 was suggested to be a Phase II *N*-methylated product of M324.
Substrate/inhibitor/inducer	*In vitro*, rucaparib was a substrate of transporters, P-gp and BCRP; a reversible inhibitor of CYP1A2, CYP2C19, CYP2C9, and CYP3A; and an inducer of CYP1A2. Furthermore, rucaparib was a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. A (b) (4) DDI trial (CO-338-044) with probes of CYP1A2, CYP2C19, CYP2C9, CYP3A, and P-gp is ongoing.
Excretion	
Primary excretion pathways	Unknown. The mass balance trial CO-338-045 is still ongoing.

10.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The applicant submitted three clinical trials and the PK data from these trials provided supportive evidence of the effectiveness of rucaparib.

Data from trials A4991014 and CO-338-010 were used to characterize rucaparib PK. Data from the part 3 of trial CO-338-010 were used to evaluate the food effect on rucaparib PK. PK data from trials A4991014, CO-338-010 and CO-338-017 were included in a population PK analyses to evaluate the effects of intrinsic and extrinsic factors on rucaparib PK. Observed exposures and the population PK

predicted exposures were used to explore exposure-response relationships. These analyses included data from trials CO-338-010 and CO-338-017.

In addition, a series of *in vitro* clinical pharmacology studies were conducted to characterize the protein binding, metabolic reaction phenotypes and enzymatic/transporter interactions of rucaparib.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The applicant proposed an oral dosing regimen of 600 mg rucaparib twice daily (BID) with or without food. Among BID dose levels of 360 mg, 480 mg, 600 mg, and 840 mg, 600 mg rucaparib BID demonstrated a favorable benefit/risk profile, with a 42% objective response rate (ORR) and a manageable safety profile in the proposed patient population. A positive relationship between AUC_{avg} and ORR over a dose range from 360 mg to 600 mg BID suggested that a lower dose may lead to a loss of efficacy. In terms of safety, positive exposure-response (E-R) relationships for adverse events (AEs) suggested that increased dose may increase the incidence of AEs. Furthermore, it is acceptable to administer rucaparib with or without food, given the mild magnitude of food effect (a 38% increase in AUC) and a large PK variability (54% for steady-state AUC).

The proposed starting dose of 600 mg rucaparib BID was also supported by the results of E-R analyses.

Exposure-efficacy analyses: Based on exposure-efficacy (E-E) analyses (**Figure 1**), there was a positive relationship between AUC_{avg} and ORR (by independent radiologist review) over the exposure range after administration of 600 mg rucaparib BID. In addition, Cox regression modeling the relationship of hazard rate of PFS and rucaparib exposure indicated that hazard ratios were 0.79 and 0.91 for 600 mg compared to 200 mg and 400 mg, respectively. Therefore, a lower dose may lead to a loss of efficacy.

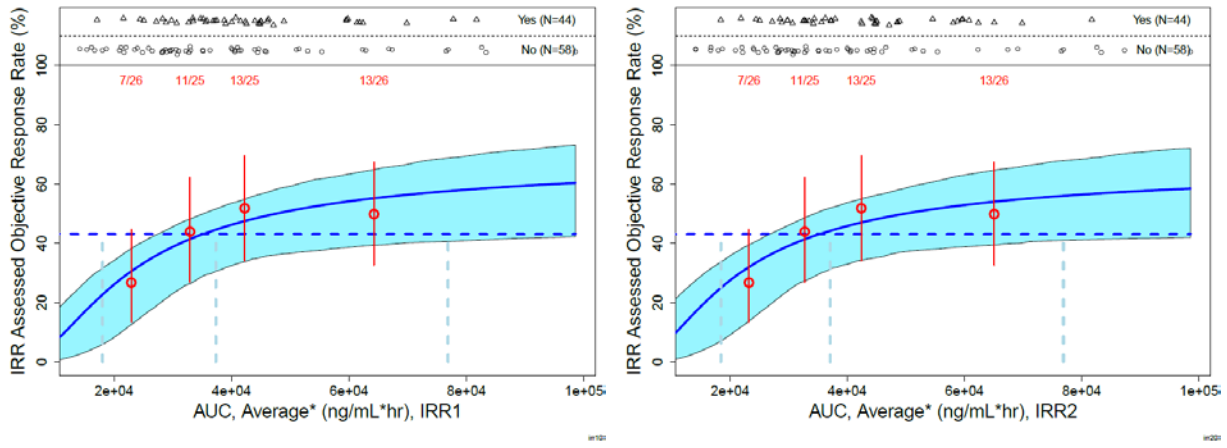


Figure 1. Exposure-efficacy Relationships for ORR by Investigator and Independent Radiologist Review

Exposure-safety analyses: Based on exposure-safety (E-S) analyses (**Figure 2**), relationships were not steep with less than 10% change in incidence of grade 3+ ALT, grade 3+ AST, grade 3+ platelet, and grade 3+ fatigue over the exposure range of 600 mg rucaparib BID. A steep E-R relationship was only

observed for the incidence of grade 2+ creatinine, which may be attribute to the inhibition of transporters, MATE1 and MATE2-K, that mediate renal excretion of creatinine. Therefore, the dose of 600 mg rucaparib BID exhibited a manageable safety profile.

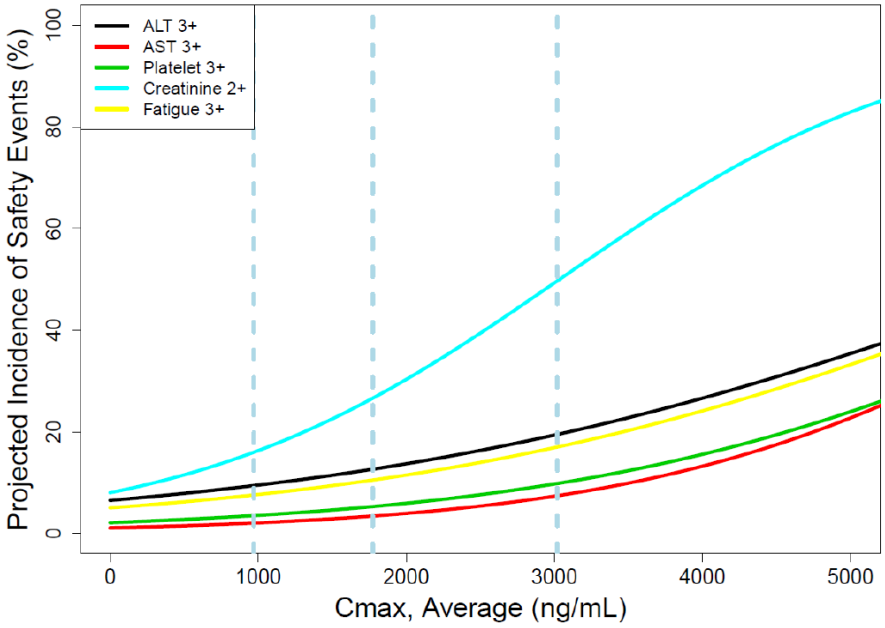


Figure 2. Exposure-safety Relationships for Adverse Events

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Hepatic impairment: Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). There were limited data (N=2) in patients with moderate hepatic impairment (total bilirubin between 1.5 times and 3 times ULN) and no data were available in patients with severe hepatic impairment (total bilirubin greater than 3 times ULN). PK and safety data were similar between patients with normal hepatic function (N=337 for PK; N=357 for safety) and patients with mild hepatic impairment (N=34 for PK; N=44 for safety). Only limited data were available in patients with moderate hepatic impairment (N=2). The ongoing mass balance trial CO-338-045 will help determine the hepatic contribution to the elimination of rucaparib. A PMR will be issued to determine the appropriate starting dose in patients with moderate hepatic impairment.

Renal impairment: Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild to moderate renal impairment (CrCL between 30 mL/min and 89 mL/min, as estimated by the Cockcroft-Gault method). No data were available in patients with severe renal impairment (CrCL less than 30 mL/min, as estimated by the Cockcroft-Gault method). The steady-state AUC of rucaparib in patients with mild (N=148) to moderate (N=72) renal impairment showed 15% and 32% higher than that in patients with normal (N=143) renal function. The

incidence of AEs was similar between patients with normal (N=155) renal function and patients with mild (N=170) to moderate (N=84) renal impairment. Dose discontinuation rate was higher in patients with moderate impairment, possibly due to poorer health status in these patients. The mass balance trial CO-338-045 is ongoing, which will help determine the renal contribution to the elimination of rucaparib.

CYP enzyme polymorphism: Based on population PK analyses, for patients taking 600 mg rucaparib twice daily, there appeared to be no significant difference in steady-state exposure of rucaparib among CYP2D6 phenotypes (poor metabolizers, N=9; intermediate metabolizers, N=69; normal metabolizers, N=75; ultra-rapid metabolizers, N=4) or between CYP1A2 normal metabolizers (N=28) and hyper-inducers (N=133).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Based on population PK analyses, concomitant treatment with proton pump inhibitors had no clinically meaningful change in steady-state exposures.

A (b) (4) DDI trial CO-338-044 with probes of CYP1A2, CYP2C19, CYP2C9, CYP3A, and P-gp is ongoing to evaluate the effect of rucaparib on other drugs in humans.

(b) (4) ongoing mass balance trial CO-338-045.

10.4. OCP Appendices

10.4.1. Bioanalysis Report

The plasma concentration of rucaparib was determined using a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometry (LC-MS/MS) method. The method validation studies defined the precision (coefficient of variation, CV) and accuracy (relative error, RE) of the bioanalytical methods, the specificity, the lower and upper limits of quantification (LLOQ and ULOQ, respectively), and the stability of rucaparib.

As shown in Table 1, three LC-MS/MS methods were validated for the quantification of rucaparib in human plasma: 1) assay A4999002 was used to measure the plasma concentration of rucaparib in study A491014; 2) assay 111066VPJ_CSC_R2 was used to measure the plasma concentration of rucaparib in study CO-338-010; 3) assay 111066VPJ_CSC_R2 was used to measure the plasma concentration of rucaparib in studies CO-338-010, CO-338-017, and CO-338-023.

Table 1. Overview of Bioanalytical Methods Used in Clinical Studies

Method Type	Analyte	Quantitation Range (ng/mL)	Internal Standard [a]	Calibration Model	Use in Clinical Study [b]	Report Number [c]
Turbo ion spray LC-MS/MS	Rucaparib	0.500 to 2,000	AG-014699-d_6	Linear weighted $1/x^2$	A4991014	A4990002
Turbo ion spray LC-MS/MS	Rucaparib	0.500 to 1,000	CO-338-d_7	Linear weighted $1/x^2$	CO-338-010	111066VPJ_CSC_R2
Turbo ion spray LC-MS/MS	Rucaparib	5.00 to 10,000	CO-338-d_7	Linear weighted $1/x^2$	CO-338-010 CO-338-017 CO-338-023	140621PVCM_CSC_R1

[a] The internal standards: AG014699-d_6 and CO-338-d_7 are the same.
[b] Only methods associated with clinical studies included in the NDA are reported here. Additional methods may be reported in supplements.
[c] Reports are included in Section 5.3.1.4.

No metabolites have been selected for analysis even though seven metabolites were proposed based on the ion spectra and rationale of biotransformation. Assessment of rucaparib metabolites is planned in the ongoing mass balance trial CO-338-045 in patients following a single oral dose of [^{14}C]-radiolabeled rucaparib.

Total plasma concentration of rucaparib was measured in all the clinical trials. Total instead of free plasma concentration measurement appears acceptable as 70.2% rucaparib was bound to human plasma proteins *in vitro*.

Assay 140621PVCM_CSC_R1 quantitatively determined rucaparib in human plasma samples following protein precipitation, then LC-MS/MS using turbo ion spray, positive ionization, and selected reaction monitoring. The calibration range for the assay was from 5.00 to 10,000 ng/mL.

The LC-MS/MS system consisted of a [redacted] (b) (4)

[redacted] (b) (4) [redacted] (b) (4) [redacted].

The LLOQ for rucaparib in human plasma was 5.00 ng/mL, while the ULOQ was 10,000 ng/mL. Chromatographic carryover was observed throughout the validation but was successfully mitigated by injecting zero samples directly after ULOQ calibration curve standard (STD) samples. The following selected reaction monitoring (SRM) transitions were used in data acquisition: rucaparib m/z 324.1 → m/z 293.1; CO-338-d_7 (internal standard) m/z 331.2 → m/z 300.2

The specificity, recovery, linearity, quantification limit, precision, and accuracy of the method were summarized below:

- Calibration standard curves: Linear regression with $1/x^2$ weighting was determined to be the best curve fit for the quantitation of CO-338 in human plasma after the first three acceptable accuracy and precision runs. Table 2 shows the parameters of calibration curve for all accepted and regressed validation runs for CO-338. The coefficient of determination (r-squared) values were greater than 0.9964.

- Accuracy and precision of calibration standards: The inter-assay RE ranged from -3.0% to 2.8% and the CV was ≤ 5.3% for all STD concentrations.

- Accuracy and precision of quality control (QC) samples: The intra- and inter-assay precision (%CV) and accuracy (%RE) of the method was assessed in three runs. Each of LLOQ QC, QC1, QC2, QC3, QC4 samples with six replicates were used for the assessment.

- The intra-assay RE ranged from -2.3% to 16.8% and the intra-assay CV was ≤ 10.0%. The inter-assay RE ranged from 2.0% to 11.2% and the inter-assay CV was ≤ 7.0% from the three accuracy and precision runs.

- Accuracy and precision of dilution quality control samples: The intra- and inter-assay accuracy and precision of the method were assessed by analyzing six replicates of a 10-fold diluted QC sample over three separate runs. The intra-assay RE ranged from 4.2% to 3.6% and the CV was ≤ 2.4%. The inter-assay RE was 0.0% and the CV was 3.7% from the three accuracy and precision runs. The accuracy and precision results obtained for the diluted QC samples demonstrated the validity of preparing samples using a 10-fold dilution factor.

- Matrix effects: The effect of different lots of matrix on the quantitation of rucaparib was evaluated at the LLOQ and ULOQ in six different lots of human plasma. One lot of hemolyzed (2% hemolysis) and one lot of lipemic human control plasma were included in the six lots. Samples were assayed in three replicates. The overall mean, CV, and RE were calculated for the multiple-lot matrix LLOQ and ULOQ samples.

- The intra-lot RE ranged from -3.4% to 5.4%; the intra-lot CV was ≤ 6.0% for the LLOQ; the intra-lot RE ranged from 1.0% to 5.0%; and the intra-lot CV was ≤5.3% for the ULOQ. The inter-lot RE was -0.4%; the inter-lot CV was 4.5% for the LLOQ; the inter-lot RE was 3.0%; and the inter-lot CV was 3.1% for the ULOQ.

- Selectivity:

    - Selectivity criteria were met in all plasma lots for CO-338-d_7 (IS). There was no response in any of the six matrix lots.

    - The selectivity of the method was also evaluated by analyzing a ULOQ STD, prepared without IS, by LC/MS/MS to monitor for possible interference from the analyte to the IS. No interference or contribution was observed from the analyte to the IS.

    - Carryover was evaluated during each regressed validation run by injecting at least one carryover blank (zero sample) after ULOQ STD samples. Carryover was observed throughout the validation but was successfully mitigated by injecting zero samples directly after ULOQ STD samples.

- Length of run assessment: The method ruggedness was established (b) (4) with intra- and inter-accuracy and precision met 20% criteria.

For assay 140621PVCM_CSC_R1, assessment of stability indicated that rucaparib was stable in human plasma for up to 8 hours at room temperature, up to 622 days (undiluted QC) or 638 days (diluted QC) at -20°C and -70°C, and after 5 freeze/thaw cycles at -20°C and at -70°C. Rucaparib was stable in human whole blood for up to 1 hour at room temperature or on ice. No significant chromatographic interferences were detected at either the retention time of the analyte or the IS.

Table 2. Stability of Rucaparib

Stability	
Benchtop (room temperature) in plasma (Low Curve Range)	24 hours[a]
Benchtop (room temperature) in plasma (High Curve Range)	8 hours
Freeze/Thaw (−20 °C) in plasma (Low Curve Range)	5 cycles[a]
Freeze/Thaw (−20 °C) in plasma (High Curve Range)	5 cycles
Freeze/Thaw (−70 °C) in plasma (Low Curve Range)	5 cycles[a]
Freeze/Thaw (−70 °C) in plasma (High Curve Range)	5 cycles
Storage (−20 °C) in plasma (Low Curve Range)	612 days[a]
Storage (−20 °C) in plasma (High Curve Range)	622 days (QC4); 638 days (DilQC) (ADDENDUM A)
Storage (−70 °C) in plasma (Low Curve Range)	377 days[a]
Storage (−70 °C) in plasma (High Curve Range)	622 days (QC4); 638 days (DilQC) (ADDENDUM A)
Whole Blood Stability (Low Curve Range)	1 hour[a]
Whole Blood Stability (High Curve Range)	1 hour
CO-338 Stock Solution at room temperature (2.5 mg/mL in methanol)	18 hours
CO-338 Stock Solution at -20 °C (2.5 mg/mL in methanol)	210 days
CO-338-d_7 Stock Solution at room temperature (100 µg/mL in methanol)	18 hours[b]
CO-338-d_7 Stock Solution at -20 °C (100 µg/mL in methanol)	210 days[b]
CO-338-d_7 Working Solution at room temperature (500 ng/mL in acetonitrile)	18 hours
CO-338-d_7 Working Solution at -20 °C (500 ng/mL in acetonitrile)	1 month[c]

[a]Reported in the low curve range validation report for human plasma (111066VPJ_CSC_R2; 1).
[b]Per Q² Solutions SOP, equivalent stock solution stability is assigned to the IS as that of the analyte because the IS is a stable-isotope labeled version of the analyte, is prepared in the same diluent, and is stored at the same temperature as that of the analyte.
[c]One month expiration assigned based on Q² Solution SOP. Stability assessments are on-going.

10.4.2. General Clinical Pharmacology

10.4.2.1. Dose/exposure-response relationships for efficacy and safety

The dose of rucaparib was initially selected based on clinical data from the dose-escalation portion (part 1) of study CO-338-010. Based on PK data and exposure-response analyses for safety and efficacy of rucaparib, 600 mg rucaparib twice daily (BID) with or without food was selected as the starting dosing regimen. Key information regarding dosing interval, dose and food effect is summarized below.

Based on PK and clinical safety data of rucaparib, BID dose was expected to be better for a desired target C_{trough} while maintaining the same safety profile compared to QD dose. In trial CO-338-010, dose levels of 40, 80, 160, 300, and 500 mg QD were evaluated in a 3+3 dose-escalation design. No patient experienced a DLT across dose levels at cycle 1. Since the desired C_{trough} of rucaparib was about 650 ng/mL based on the meta-analysis of the Phase 1/2 PK, safety, and efficacy data of olaparib and niraparib, not all the patients achieved the desired C_{trough}. Compared to QD administration of rucaparib, BID dose was expected to result in a lower C_{max} and higher C_{trough}. In addition, PK modeling confirmed that BID dose would help achieve the desired C_{trough}.

After selecting BID dose, 3+3 dose-escalation study was continued at dose levels of 360 mg, 480 mg, 600 mg, and 840 mg, among which 600 mg BID was selected for further development. Table 3 and Table 4 show the summary of treatment-related grade 3+ treatment-emergent adverse events (TEAEs) and dose modification in study CO-338-010. In terms of safety, no patient at any BID dose level discontinued rucaparib due to a treatment-related AE, and none of 7 patients experienced a DLT at dose level of 600 mg BID. In terms of efficacy, Table 5 shows that RECIST responses were observed at doses of 360 mg BID and above, but due to the small number of patients, no definitive relationship between dose and response was concluded. In addition, all patients treated with 600 mg BID had at least 2 times the desired target C_{trough}.

Table 3. Treatment-related Grade 3+ TEAEs in Study CO-338-010

SOC PT	40-500 mg QD (N=26)	240 mg BID (N=3)	360 mg BID (N=8)	480 mg BID (N=9)	600 mg BID (N=7)	840 mg BID (N=3)	Overall (N=56)
	n (%)						
Any Treatment-related ≥ Grade 3 TEAE	1 (3.8)	1 (33.3)	2 (25.0)	3 (33.3)	3 (42.9)	1 (33.3)	11 (19.6)
Combined Anemia, Low/Decreased Hemoglobin	**0**	**0**	**1 (12.5)**	**2 (22.2)**	**2 (28.6)**	**0**	**5 (8.9)**
Anaemia	0	0	1 (12.5)	2 (22.2)	2 (28.6)	0	5 (8.9)
Combined Asthenia/Fatigue	**0**	**1 (33.3)**	**0**	**0**	**0**	**1 (33.3)**	**2 (3.6)**
Fatigue	0	1 (33.3)	0	0	0	1 (33.3)	2 (3.6)
Combined Neutropenia, Low/Decreased ANC	**1 (3.8)**	**0**	**0**	**1 (11.1)**	**0**	**0**	**2 (3.6)**
Neutropenia	1 (3.8)	0	0	1 (11.1)	0	0	2 (3.6)
Combined Thrombocytopenia, Low/Decreased Platelets	**0**	**0**	**0**	**1 (11.1)**	**1 (14.3)**	**0**	**2 (3.6)**
Thrombocytopenia	0	0	0	1 (11.1)	1 (14.3)	0	2 (3.6)

Source: Table 14.3.1.1.9.1.
Abbreviations: BID = twice daily; N or n = number of patients; PT = Preferred Term; QD = once daily; SOC = System Organ Class; TEAE = treatment-emergent adverse event.
Note: Combined terms, then SOCs and PTs, are presented in terms of descending incidence.

Table 4. Summary of Rucaparib Discontinuation, Dose Reduction, and Treatment Interruption

SOC PT	40-500 mg QD (N=26)	240 mg BID (N=3)	360 mg BID (N=8)	480 mg BID (N=9)	600 mg BID (N=7)	840 mg BID (N=3)	Overall (N=56)
Number of Patients with at Least 1	**n (%)**						
TEAE that led to discontinuation of study drug	4 (15.4)	3 (100.0)	2 (25.0)	1 (11.1)	1 (14.3)	0	11 (19.6)
Treatment-related TEAE that led to discontinuation of study drug	0	0	0	0	0	0	0
TEAE that led to study drug dose reduction	2 (7.7)	0	1 (12.5)	3 (33.3)	4 (57.1)	1 (33.3)	11 (19.6)
Treatment-related TEAE that led to study drug dose reduction	2 (7.7)	0	1 (12.5)	3 (33.3)	4 (57.1)	1 (33.3)	11 (19.6)
TEAE that led to study drug interruption	4 (15.4)	2 (66.7)	2 (25.0)	2 (22.2)	4 (47.1)	1 (33.3)	15 (26.8)
Treatment-related TEAE that led to study drug interruption	2 (7.7)	1 (33.3)	2 (25.0)	2 (2.2)	4 (57.1)	1 (33.3)	12 (21.4)

Source: Table 14.3.1.1.1.1
Abbreviations: BID = twice daily; N or n = number of patients; PT = Preferred Term; QD = once daily; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Table 5. Summary of Efficacy at 240 mg or Higher Rucaparib

Response Parameter(s)	240 mg BID (N=3)	360 mg BID (N=8)	480 mg BID (N=9)	600 mg BID (N=7)	840 mg BID (N=3)
Efficacy in All Patients Evaluable by RECIST v1.1					
# of Patients with ≥1 Target Lesion at Baseline	N=2	N=7	N=9	N=6	N=3
ORR (%) by RECIST v1.1 (Best Single Response)	0	29	33	33*	0
ORR (%) by RECIST v1.1 (Confirmed Response)	0	29	33	17	0
Efficacy in All BRCA-mutant Patients Evaluable by RECIST v1.1					
# of Patients with a BRCA Mutation and ≥ 1 Target Lesion at Baseline	N=0	N=6	N=8	N=6	N=1
ORR (%) by RECIST v1.1 (Best Single Response)	NA	33	38	33*	0
ORR (%) by RECIST v1.1 (Confirmed)	NA	33	38	17	0
Efficacy in All BRCA-mutant Patients Evaluable by RECIST v1.1 and/or GCIG CA-125 Criteria					
# of Patients with BRCA mutation and ≥1 Target Lesion and/or CA-125 > 2x ULN at Baseline	N=0	N=7	N=8	N=6	N=1
ORR (%) by RECIST v1.1 (Best Single Response) and/or CA-125	NA	43	38	67*	0
ORR (%) by RECIST v1.1 (Confirmed) and/or CA-125	NA	43	38	50	0

*includes 1 patient with an unconfirmed PR

10.4.2.2. Pharmacokinetic characteristics of the drug and its major metabolites

The pharmacokinetics (PK) of rucaparib was evaluated in patients in clinical trials A4991014 and CO-338-010. The highlights of single-dose and multiple-dose PK of rucaparib are summarized below:

- The mean AUC accumulation ratios at steady state ranged from 1.6 to 2.3 and 3.5 to 6.2 for QD and BID doses, respectively.

- Based on the power model for pooled PK data and plots of C_{max} or $AUC_{0-\tau}$ by different dose levels, the steady-state C_{max} and $AUC_{0-\tau}$ for both QD and BID rucaparib were generally dose proportional.

- At dose level of 600 mg BID, the mean steady-state C_{max} and AUC_{0-12} were 1940 ng/mL (54% CV) and 16900 ng·hr/mL (54% CV), respectively (Figure 1). The median T_{max} was 1.9 hour with a range from 0 to 6 hour. The steady-state C_{max}/C_{trough} ratio was about 1.2.

The single-dose (day 1) and steady-state (day 15) PK parameters of rucaparib following QD and BID doses were summarized in Table 6.

Table 6. Single-dose and Steady-state Plasma PK Parameters of Rucaparib following QD or BID Administration

Dosage	N	Day	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\tau}$ (ng·hr/mL)	CL_{ss}/F (L/hr)	AR	$T_{1/2}$ (hr)
40 mg QD	3	1	129 (28)	2.5 (1-4)	915[b]	NR	NA	13.9 (57)
		15	138 (36)	4 (1-4.05)	1810 (44)	26.7 (59)	1.68[b]	25.7 (23)
80 mg QD	3	1	114 (41)	1.5 (1-2.5)	800 (27)	NR	NA	11.0[b]
		15	175 (37)	2.5 (2.5-2.57)	1740 (20)	47.5 (23)	2.33 (42)	19.5[b]
160 mg QD	4	1	261 (51)	4.0 (4-6.05)	3050 (51)	NR	NA	19.9 (21)
		15	288 (29)[c]	3.75 (2.5-4)[c]	4110 (33)[c]	41.6 (29)[c]	1.84 (31)[c]	33.6 (12)[c]
300 mg QD	3	1	629 (37)	2.5 (1-4.08)	5740 (38)	NR	NA	15.2 (72)
		15	693 (76)	2.53 (2.5-8)	9610 (83)	46.7 (63)	1.6 (53)	29.8[b]
500 mg QD	3	1	949 (52)	4 (4-4)	11000 (61)	NR	NA	15.0 (32)
		15	1390 (23)	4 (4-4.17)	19900 (41)	27.8 (35)	1.94 (17)	20.8 (38)
240 mg BID	3	1	219 (72)	6 (4.05-6)	2800[a]	NR	NA	NR[b]
		15	971 (49)	1.5 (1-4)	10700[b]	27.3[b]	5.44[a]	
360 mg BID	8	1	666 (58)	3.23 (1.5-6)	4860 (58)[f]	NR	NA	
		15	1300 (43)[f]	3.3 (0-6.33)[f]	9430[b]	40.4[b]	4.08[b]	
480 mg BID	9	1	1150 (57)	2.5 (1.5-4)	8810 (63)[g]	NR	NA	
		15	3170 (69)[g]	1.51 (0-6)[g]	26300 (73)[f]	26.2 (63)[f]	3.97 (38)[e]	
600 mg BID	7	1	1030 (61)	4 (2.42-10)	7200 (66)[d]	NR	NA	
		15	2420 (45)	4 (2.53-10)	21400 (61)[d]	58.6 (123)[d]	3.23 (66)[d]	
840 mg BID	3	1	1380 (69)	4 (2.5-8)	13200[b]	NR	NA	
		15	3030 (NR)[b]	4.04 (4-4.07)[b]	29000[a]	29[a]	1.47[a]	

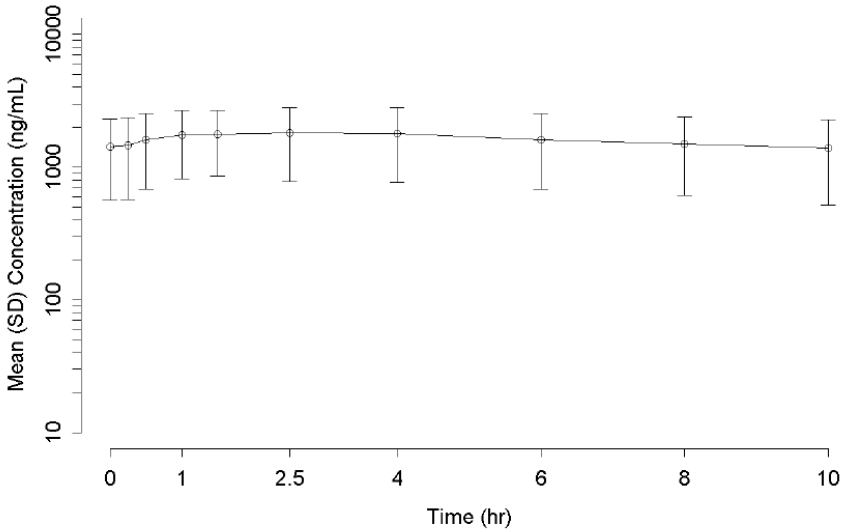
Source: Table 10-3. Study CO-338-010 CSR, Appendix 16.1.17

Abbreviations: AR = accumulation ratio based on AUC; $AUC_{0-\tau}$ = area under the plasma concentration-time curve from 0 to the end of dosing interval (τ=24 hr for QD; τ=12 hr for BID; for BID dosing, concentration at 12 hr was calculation by extrapolation from last observed concentration in the same dosing interval); BID = twice daily; CL_{ss}/F = apparent steady state clearance; C_{max} = maximum plasma concentration; NA = not available; NR = not reportable; QD = once daily; $T_{1/2}$ = half-life; T_{max} = time of occurrence of C_{max}.

Arithmetic mean (CV%) for all PK parameters except median (range) for T_{max}.

[a] n = 1; [b] n = 2; [c] n = 3; [d] n = 4; [e] n = 5; [f] n = 6; [g] n = 8

[b] $T_{1/2}$ is too long to allow for accurate estimate in BID dosing.



Source: Redrawn from Figure 10-16. Study CO-338-010 CSR, Appendix 16.1.17
Abbreviations: BID = twice daily; SD = standard deviation

Figure 1. Steady-state (Day 15) Rucaparib Plasma Concentration over Time in Study CO-338-010

Pharmacokinetics of major metabolites

The PK of rucaparib metabolites has not been characterized. Current understanding of the metabolites suggests that they are the products of Phase II metabolic reactions, which generally result in less active pharmacologically and toxicologically compounds.

Drug absorption

The mean oral bioavailability following a single oral dose of 12 to 120 mg rucaparib was 36% (Table 7). The mean oral bioavailability values of rucaparib at doses > 480 mg with a high-fat meal, under fasted conditions, and with a meal of patient's choice were 51.7%, 32.6%, and 37.2%, respectively.

Table 7. Bioavailability of Rucaparib Following Single Oral Dose

	Rucaparib Dose (mg)					
	12 mg	36 mg	48 mg	72 mg	80 mg	120 mg
N	3	8	8	6	4	4
Oral bioavailability (%)	33.4 (13.8)	45.3 (37.8)	33.6 (53.5)	30.1 (33.3)	30.7 (52.4)	41.1 (26.1)

Based on population PK analyses, patients receiving concomitant proton pump inhibitors (PPIs) (N=161) had about 15% higher absolute bioavailability than patients without concomitant PPIs (N=292). Concomitant treatment with PPIs has no clinically meaningful change in steady-state exposures.

Following rucaparib of 40 to 500 mg QD and 240 to 840 mg BID, the C_{max} and $AUC_{0-\tau}$ of rucaparib were generally dose proportional. The median T_{max} ranged from 1.5 to 6 hours.

A high-fat meal increased rucaparib AUC_{0-24h} by 38% and C_{max} by 20%, and delayed T_{max} by a median of 2.5 hours.

Drug distribution

Plasma protein binding

In vitro, rucaparib was 70.2% bound to human plasma proteins at clinical exposures.

Blood to plasma ratio

In vitro, [^{14}C]-radiolabeled rucaparib was preferentially distributed into red blood cells with a blood to plasma ratio of 1.8 at 0.1, 1, and 10 µM. The mass balance trial CO-338-045 in patients is ongoing.

P-Glycoprotein

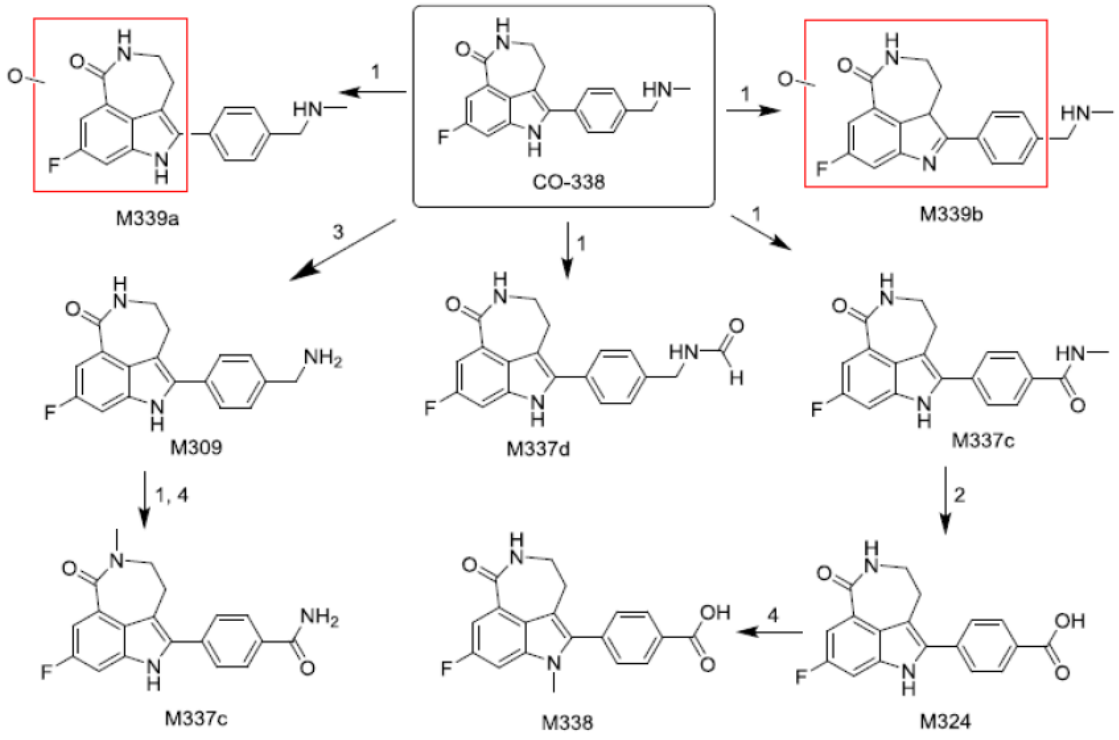
In vitro, rucaparib was a substrate of P-glycoprotein (P-gp).

Volume of distribution

The mean V_{ss} of rucaparib was 211 L (ranging from 113 to 262 L) following a single IV dose of 12 to 40 mg. The mass balance trial CO-338-045 in patients is ongoing.

Drug metabolism

In part 1 of study CO-338-010, plasma samples from 3 patients treated with 600 mg rucaparib camsylate (no [^{14}C]-radiolabel) BID were collected on day 15 for metabolites profiling. The biotransformation pathways for rucaparib were suggested to be hydroxylation, oxidation, deamination, *N*-demethylation, and Phase II methylation (Figure 2).



Source: Figure 1, Report 130808.03 (Appendix 16.1.18 to CSR CO-338-010)
Note: 1. Hydroxylation or oxidation; 2. Deamination; 3. N-demethylation; 4. Phase II methylation
Two metabolites (M337c) had the same HPLC retention time.
Red box for M339a and M339b indicates uncertainty of the oxidation site.

Figure 2. Proposed Biotransformation Pathway of Rucaparib in Cancer Patients

The relative abundance of each proposed metabolite was estimated by comparing the metabolite's peak area with the sum of all rucaparib-related peak areas. Rucaparib, M324, and M338 were the major circulating drug-related identities in patient plasma, accounting for about 43.5% to 55.1%, 16.8% to 20.0%, and 12.8% to 24.9% of the total rucaparib-related peak area, respectively (Table 8). M324 was a carboxylic acid and M338 was suggested to be a Phase II *N*-methylated product of M324. Additional metabolites, M337c and M337d, underwent oxidation, *N*-demethylation, and/or *N*-methylation products, accounting for 2.03% to 2.27% and 6.83% to 8.96% of the total rucaparib-related peak area, respectively. Minor metabolites M339a and M339b were hydroxylation or oxidation products, accounting for less than 1.6% of the total peak area, respectively. Another minor metabolite, M309, was *N*-demethylated rucaparib, accounting for less than 1.02% of the total peak area. Further assessment of rucaparib metabolites is planned in the ongoing mass balance study CO-338-045 in patients following a single oral dose of [^{14}C]-radiolabeled rucaparib.

Table 8. Relative Amount of Detected Metabolites and Rucaparib from Pooled Plasma following 600 mg Rucaparib BID for 2 weeks

Metabolite	Mean%	%CV
M339a	1.41%	13.83%
M339b	0.53%	32.17%
M309	0.81%	29.52%
M337c	2.19%	6.21%
M337d	8.10%	13.84%
M324	18.40%	8.70%
M338	18.03%	34.45%
Rucaparib	50.53%	12.23%

Source: Table 3, Report 130808.03 (Appendix 16.1.18 to CSR CO-338-010)
Abbreviations: BID = twice daily, CV = coefficient of variation n = 3

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib.

In vitro evaluations

CYP phenotyping using human liver microsomes

In vitro rucaparib was metabolized in human liver microsomes (HLMs) with a low metabolic turnover rate. Thus, the *in vitro* investigation of CYP mediated rucaparib metabolism employed the incubation of rucaparib with human recombinant CYPs. As shown in Table 9**Table**, results indicated that CYP2D6 and to a lesser extent, CYP1A2 and CYP3A4, had the ability to metabolize rucaparib.

Table 9. Metabolism of Rucaparib by Human Recombinant CYP Enzymes

CYP Isoform	Percent Metabolism (%)	
	1 µM Rucaparib	5 µM Rucaparib
CYP1A2	24.00	17.19
CYP2A6	1.00	0.00
CYP2B6	1.00	0.00
CYP2C8	1.93	0.00
CYP2C9*1	5.95	0.00
CYP2C9*2	0.00	0.00
CYP2C19	0.00	0.00
CYP2D6	54.86	42.67
CYP2E1	0.00	0.00
CYP3A4	12.92	8.42
CYP3A5	0.00	0.00

CYP phenotyping

The role of CYPs involved in rucaparib oxidative metabolism was investigated in 30-minute incubations with 11 human recombinant CYP enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C9*2, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

CYP reaction phenotyping

Results indicated that CYP2D6 (55% and 43% metabolism at 1 µM and 5 µM, respectively) and, to a lesser extent, CYP1A2 (24% and 17% metabolism at 1 µM and 5 µM, respectively) and CYP3A4 (13% and 8% metabolism at 1 µM and 5 µM, respectively) had the ability to metabolize rucaparib.

Metabolic stability and metabolite profiling

The profiling of rucaparib metabolites by incubation with cryopreserved hepatocytes resulted in the preliminary identification of an *N*-demethylated derivative in dog, while oxidative deamination leading to the formation of a carboxylic acid metabolite was also identified in rat, dog, monkey, and human. The *in vitro* data suggested that metabolite production in rats, dogs and humans would be similar, and supported selection of the rat and dog as the species for the nonclinical safety pharmacology and toxicology studies. The *N*-demethylated metabolite and the oxidative deamination metabolite were later observed *in vivo* and named as M309 and M324, respectively.

In vivo evaluations

The mass balance trial CO-338-045 in patients is ongoing. The biotransformation pathways for rucaparib were characterized as hydroxylation, oxidation, deamination, *N*-demethylation, and Phase II methylation.

Rucaparib, M324, and M338 were the major circulating drug-related identities in patient plasma. M324 was a carboxylic acid and M338 was suggested to be a Phase II *N*-methylated product of M324. Additional metabolites, M337c and M337d, underwent oxidation, *N*-demethylation, and/or *N*-methylation products. Minor metabolites M339a and M339b were hydroxylation or oxidation products. Another minor metabolite, M309, was *N*-demethylated rucaparib.

Drug elimination and excretion

Elimination

In vitro data suggested slow metabolism by CYP enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib.

The mass balance trial CO-338-045 in patients is ongoing.

Clearance

Following a single IV dose of 12 to 40 mg rucaparib, the CL ranged from 13.9 to 18.4 L/hour.

Half-Life ($T_{1/2}$)

Following a single IV dose of 12 to 40 mg rucaparib, the median $T_{1/2}$ was 17 hours. Following a single oral dose of 40 to 500 mg rucaparib, the $T_{1/2}$ ranged from 11 to 29.8 hrs.

Dose proportionality assessment

Dose proportionality following single dose of rucaparib

Rucaparib demonstrated linear PK over an oral QD dose range from 40 to 500 mg and an oral BID dose range from 240 to 840 mg.

In study A4991014, following a 30-min single dose IV infusion of 12 to 40 mg, the C_{max} and AUC_{inf} were generally dose proportional (Figure 3**Figure**).

The slopes [90% CI] of the power model on a logarithmic scale were 1.22 [1.07, 1.37] for C_{max} (p-value < 0.001) and 1.18 [0.96, 1.40] for AUC_{inf} (p-value < 0.001).

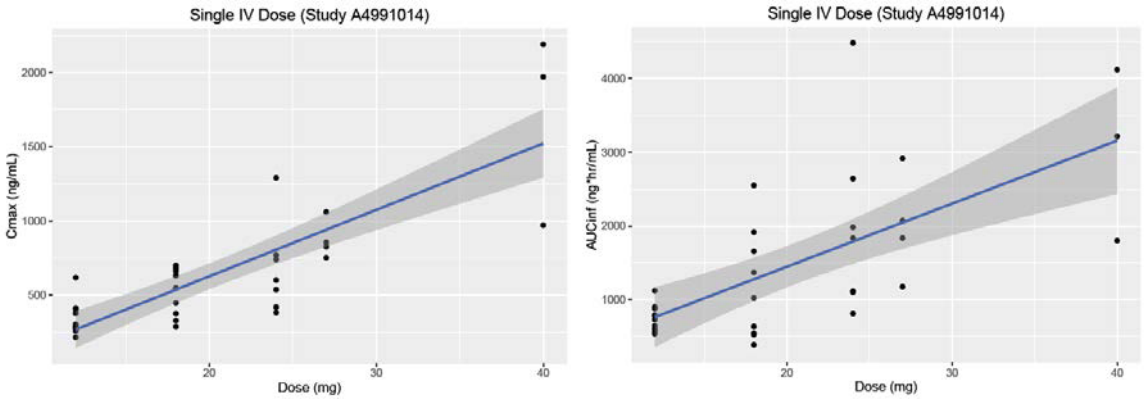


Figure 3. C_{max} and AUC_{inf} across Doses Following a Single IV Rucaparib

In study CO-338-010, following a single oral dose of 12 to 360 mg, the C_{max} and AUC_{inf} were generally dose proportional (Figure 4).

The slopes [90% CI] of the power model on a logarithmic scale were 1.03 [0.95, 1.10] for C_{max} (p-value < 0.001) and 1.15 [1.05, 1.24] for AUC_{inf} (p-value < 0.001).

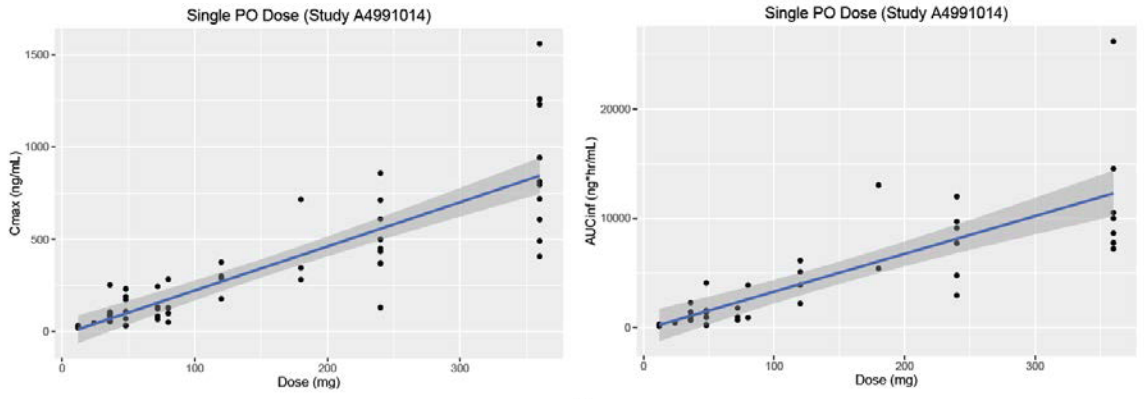


Figure 4. C_{max} and AUC_{inf} across Doses Following a Single Oral Rucaparib

Dose proportionality following multiple doses of rucaparib

Following continuous daily oral doses of 80 to 360 mg for 14 days (study A4491014) and daily oral doses of 40 to 500 mg for 15 days (part 1 of study CO-338-010), the C_{max} and AUC_{0-24} were generally dose proportional (Figure 5).

The slopes [90% CI] of the power model on a logarithmic scale were 1.00 [0.89, 1.10] for C_{max} (p-value < 0.001) and 1.11 [0.99, 1.23] for AUC_{0-24} (p-value < 0.001).

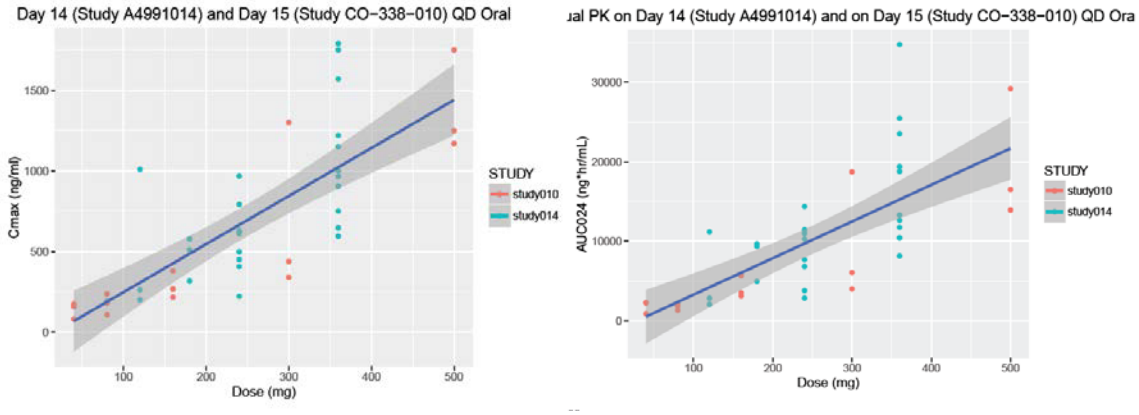


Figure 5. Steady-state (Day 14) C_{max} and AUC_{0-24} across Doses Following Continuous Oral QD Rucaparib

Following continuous BID oral doses of 240 to 840 mg for 15 days (study CO-338-010 part 1), the C_{max} and AUC_{0-12} were generally dose proportional (Figure 6).

The slopes [90% CI] of the power model on a logarithmic scale were 1.03 [0.68, 1.38] for C_{max} (p-value < 0.001) and 1.04 [0.68, 1.41] for AUC_{0-12} (p-value < 0.001).

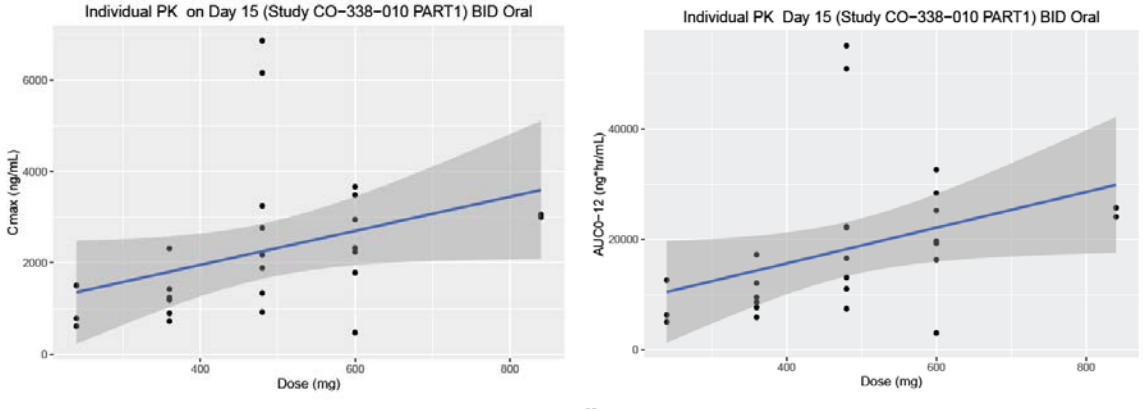


Figure 6. Steady-state (Day 15) C_{max} and AUC_{0-12} across Doses Following a Continuous Oral BID Rucaparib

In summary, based on the power model for pooled PK data and plots of C_{max} or $AUC_{0-\tau}$ by different dose levels, the steady-state C_{max} and $AUC_{0-\tau}$ for both QD (40 – 500 mg) and BID (240 – 840 mg) were generally dose proportional.

Time-independent PK

PK of rucaparib is time-independent.

A plot of the observed steady-state C_{trough} of rucaparib by treatment cycles was generated using pooled data from studies CO-338-010 (up to cycle 9) and CO-338-017 (up to cycle 4). As shown in Figure 7, a total of 1370 C_{trough} concentrations from 370 patients were included. The analysis indicated a slight reduction in rucaparib C_{trough} over time. This decreasing trend was expected due to dose modifications over time in some patients.

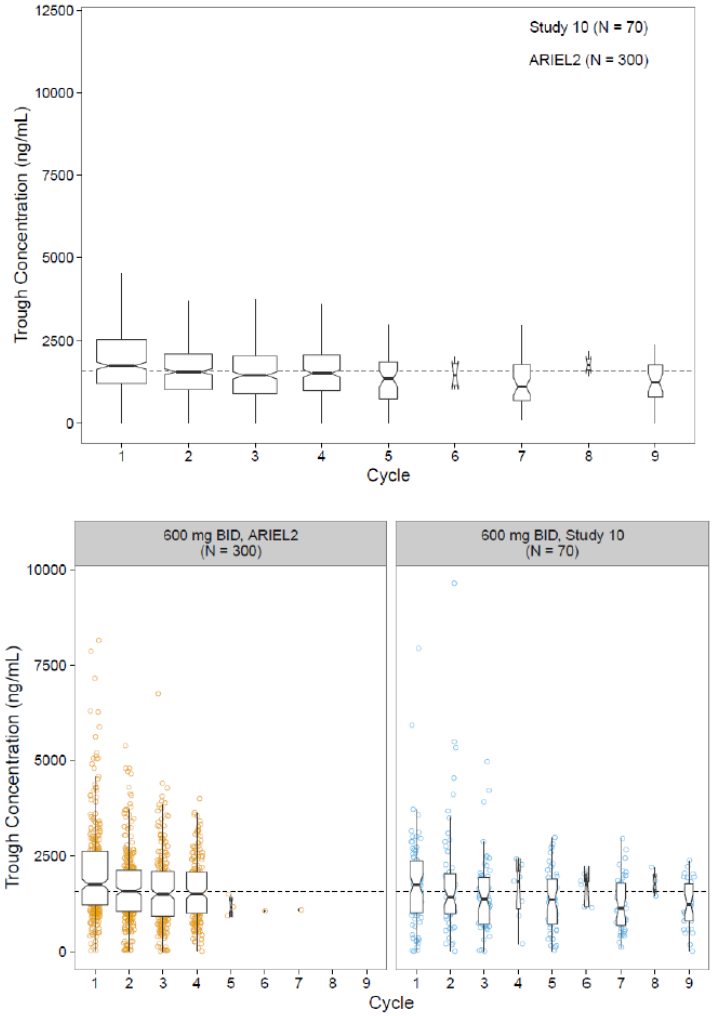


Figure7. Boxplots of Trough Concentrations by Cycle in Patients Initiating Treatment with 600 mg Rucaparib BID

Inter- and intra-subject variability of PK parameters in volunteers and patients

Rucaparib has only been investigated in patients.

High variability of rucaparib PK parameters has been observed in patients. Following multiple oral rucaparib doses from 240 to 840 mg BID, the CVs of C_{max} and AUC_{0-12} ranged from 43% to 72% and 58% to 73% across different dose levels, respectively. In a 2 by 2 crossover food effect study in 26 patients taking 600 mg rucaparib BID, the CVs of C_{max} and AUC_{0-12} ranged from 73% to 84% and 74% to 76%, respectively.

Based on population PK analyses, the inter-individual variability (IIV) on the apparent oral clearance of rucaparib was estimated 48.8%.

The variability may be attributable to the variation in intrinsic factors and extrinsic factors of patients.

10.4.2.3. Intrinsic factor assessments

Hepatic impairment

No dedicated trial has been conducted in patients with hepatic impairment. The mass balance trial CO-338-045 is ongoing. Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild hepatic impairment. There were limited data (N=2) in patients with moderate hepatic impairment and no data were available in patients with severe hepatic impairment. A PMR will be issued for the determination of appropriate starting dose of rucaparib in patients with moderate hepatic impairment. The following summary is based on the available safety and efficacy data of rucaparib.

Safety:

A total of 46 patients with hepatic impairment were enrolled at study entry, among which 44 patients were classified with mild hepatic impairment and 2 patients were classified with moderate hepatic impairment. Due to the limited number of patients with moderate impairment, a separate analysis of these patients was not conducted.

In general, there is no significant difference in incidence of treatment-emergent adverse events (TEAEs), dose modification or deaths in patients with hepatic impairment (N=46) as compared to those with normal hepatic function (N=357). The incidence of treatment-related TEAEs was 91.3% of patients with hepatic impairment and 95.3% of patients without hepatic impairment. The incidence of serious adverse events (SAEs) was 39.1% of patients with hepatic impairment and 28.1% of patients without hepatic impairment. There was no significant difference in the occurrence of grade 3+ TEAEs (63.0% of patients with hepatic impairment; 61.7% of patients without hepatic impairment). TEAEs that led to treatment interruption and/or dose reduction occurred at a lower rate in patients with hepatic impairment than in patients without hepatic impairment (56.5% vs 65.3%). TEAEs led to discontinuation of rucaparib in 23.9% of patients with hepatic impairment and in 17.9% of patients without hepatic impairment. A TEAE with an outcome of death was reported in 4 patients (8.7%) with hepatic impairment and in 10 patients (2.8%) without hepatic impairment.

Efficacy:

As shown in **Error! Reference source not found.**0, there was no notable difference in efficacy between patients with hepatic impairment as compared to those with normal hepatic function.

Table 10. Confirmed Response Rate per Independent Radiologist Reviewer by Hepatic Impairment Safety Population

	Hepatic Impairment 600 mg BID (N=12)	No Hepatic Impairment 600 mg BID (N=94)	Total 600 mg BID (N=106)
Confirmed Response Rate	6 / 12 (50.0%)	38 / 94 (40.4%)	44 / 106 (41.5%)
95% CI	21.1 - 78.9%	30.4 - 51.0%	32.0 - 51.5%
Best Overall Confirmed Response			
CR	1 / 12 (8.3%)	4 / 94 (4.3%)	5 / 106 (4.7%)
PR	5 / 12 (41.7%)	34 / 94 (36.2%)	39 / 106 (36.8%)
SD	2 / 12 (16.7%)	38 / 94 (40.4%)	40 / 106 (37.7%)
Discontinued	2	21	23
Ongoing	0	17	17
PD	4 / 12 (33.3%)	13 / 94 (13.8%)	17 / 106 (16.0%)
NE	0 / 12 (0.0%)	5 / 94 (5.3%)	5 / 106 (4.7%)
Response by RECIST or GCIG CA-125			
Yes	7 (58.3%)	62 (66.0%)	69 (65.1%)
95% CI	27.7 - 84.8%	55.5 - 75.4%	55.2 - 74.1%
No	5 (41.7%)	28 (29.8%)	33 (31.1%)
Inevaluable	0	4 (4.3%)	4 (3.8%)

Note: The 95% confidence intervals are Clopper-Pearson intervals which are exact intervals with coverage probability of at least 95%.

Renal impairment

No dedicated trial has been conducted in patients with renal impairment. The mass balance trial CO-338-045 is ongoing. Based on population PK analyses and clinical safety data of rucaparib, no dose adjustment is recommended for patients with mild to moderate renal impairment. No data were available in patients with severe renal impairment. The following summary is based on the available safety and efficacy data of rucaparib.

Safety:

Based on the FDA criteria, among the 409 patients included in the safety population, 155 patients were classified with normal renal function, 170 patients were classified with mild renal impairment, and 84 patients were classified with moderate renal impairment at study entry.

As shown in Table 11, the incidence of TEAEs was similar between patients with normal renal function and patients with mild to moderate renal impairment. Dose discontinuation rate was higher in patients with moderate renal impairment, possibly due to poorer health status in these patients.

Table 11. Safety Data of Rucaparib by Renal Function

AE / Dose Modifications	Normal Renal Function (N=155)	Mild Renal Impairment (N=170)	Moderate Renal Impairment (N=84)
Treatment-related TEAE	96.1%	92.4%	97.6%
Severe AE	25.2%	31.8%	32.1%
Grade 3+ TEAE	55.5%	64.1%	69%
Deaths	3.9% (6/155)	1.8% (3/170)	6.0% (5/84)
TEAE leading to Dose interruption/reduction	52.9%	71.8%	70.2%
TEAE leading to Dose discontinuation	14.2%	17.6%	28.6%

Efficacy:

As shown in Table 12, there was no notable difference in efficacy between patients with mild to moderate renal impairment as compared to those with normal renal function.

Table 12. Confirmed Response Rate per Independent Radiologist Reviewer by Renal Impairment Safety Population

	Renal Impairment 600 mg BID (N=66)	No Renal Impairment 600 mg BID (N=40)	Total 600 mg BID (N=106)
Confirmed Response Rate	31 / 66 (47.0%)	13 / 40 (32.5%)	44 / 106 (41.5%)
95% CI	34.6 - 59.7%	18.6 - 49.1%	32.0 - 51.5%
Best Overall Confirmed Response			
CR	4 / 66 (6.1%)	1 / 40 (2.5%)	5 / 106 (4.7%)
PR	27 / 66 (40.9%)	12 / 40 (30.0%)	39 / 106 (36.8%)
SD	21 / 66 (31.8%)	19 / 40 (47.5%)	40 / 106 (37.7%)
Discontinued	12	11	23
Ongoing	9	8	17
PD	10 / 66 (15.2%)	7 / 40 (17.5%)	17 / 106 (16.0%)
NE	4 / 66 (6.1%)	1 / 40 (2.5%)	5 / 106 (4.7%)
Response by RECIST or GCIG CA-125			
Yes	43 (65.2%)	26 (65.0%)	69 (65.1%)
95% CI	52.4 - 76.5%	48.3 - 79.4%	55.2 - 74.1%
No	20 (30.3%)	13 (32.5%)	33 (31.1%)
Inevaluable	3 (4.5%)	1 (2.5%)	4 (3.8%)

Note: The 95% confidence intervals are Clopper-Pearson intervals which are exact intervals with coverage probability of at least 95%.

10.4.2.4. Extrinsic factor assessments

Food effect

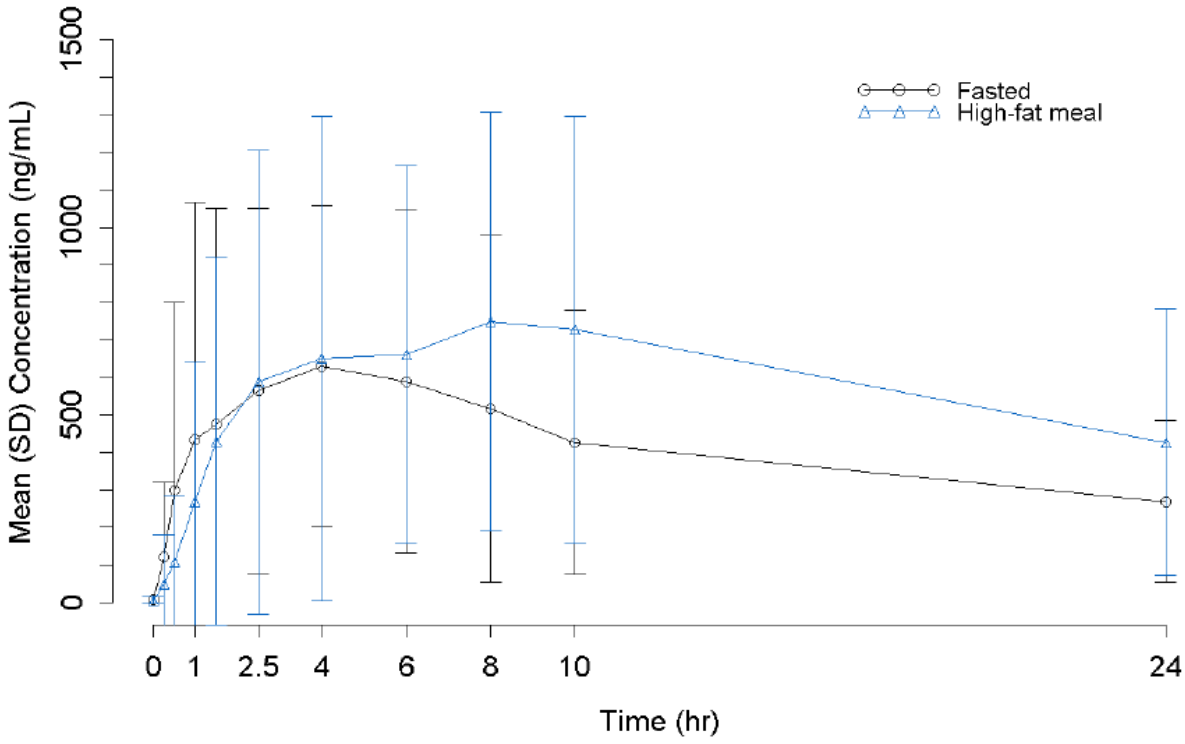
Systemic exposure of rucaparib increased when administered with food, however, given the mild magnitude of food effect (a 38% increase in AUC) and a large PK variability (54% CV for steady-state AUC), rucaparib was taken with or without food.

Food effect in patients:

Study CO-338-010 is an ongoing 3-part Phase 1/2, open label, safety, PK, and preliminary efficacy study of oral rucaparib. The food effect was evaluated in 26 patients in part 3, and the major cancer types were ovarian cancer (53.8%) and breast cancer (11.5%). Patients were randomized and received a single dose of 600 mg rucaparib on day -7 (with a high-fat meal or under a fasted status) and a single dose of 600 mg rucaparib on day 1 (under the opposite condition). PK samples were collected prior to dosing and from 15 minutes to 10 hours after dosing on day -7 and day 1.

The results showed a high-fat meal increased C_{max} and AUC_{0-24} by about 20% and 38%, respectively. In addition, a high-fat meal delayed T_{max} by approximately 2.5 hours. Overall, the food effect on rucaparib PK is low to moderate given the relatively high PK variability.

The mean (SD) rucaparib plasma concentration-time profile by meal status was shown in Figure 8.



Source: Redrawn from Figure 10-13. Study CO-338-010 CSR, Appendix 16.1.17
Abbreviations: SD = standard deviation; hr = hour; ng = nanogram; mL = milliliter

Figure 8. Rucaparib Plasma Concentration versus Time Following a Single Dose of 600 mg Rucaparib with or without Food (Study CO-338-010 Part 3)

10.4.3. **Pharmacometrics Population PK Analysis**

10.4.3.1. Sponsor's Population PK analysis

The primary objectives of this analysis were to:

• To describe the rucaparib PK time course, variability, and covariates influencing rucaparib PK variability.

• To obtain Bayesian post hoc rucaparib PK parameter estimates for patients in ARIEL2 (Part 1 and Part 2) and Study 10 (Parts 1, 2A, and 3).

• To estimate rucaparib PK exposures for inclusion in the analysis of exposure-response for safety and efficacy.

Data

This PPK analysis was conducted to evaluate rucaparib PK data obtained from three clinical studies (A4991014, Study CO-338-010, and ARIEL2). The summary of the studies and covariates evaluated are provided in Table 3.

Table 3: Summary of Studies included in Population PK Analysis

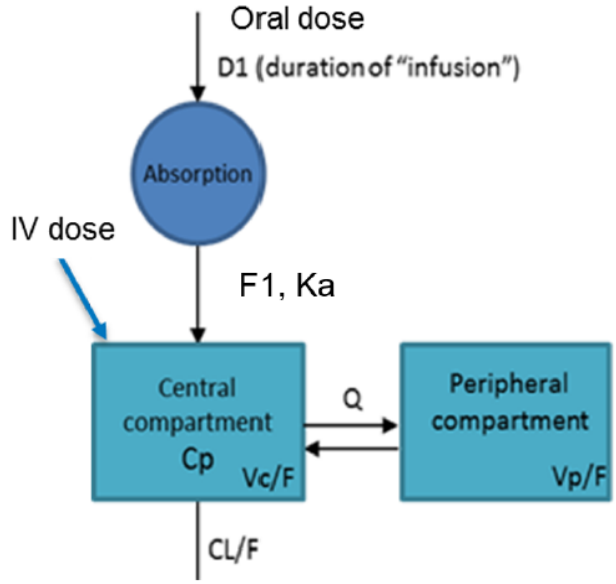
Study Identifier	Description and Key Objectives	N Patients	Sampling Design
Study 10 Phase 1/2 Non-randomized open-label	**Part 1** (Phase 1 portion): Evaluate safety and PK, and determine MTD	56	oral rucaparib, 40 to 500 mg QD to 240 to 840 mg BID cycle 1, day 1 and 15: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose cycle 1, day 8 and 22, and day 1 of cycles 3-9: pre-dose food effect at 40 and 300 mg: Day -7 (fasted) and Cycle 1 Day 1 (high-fat meal): pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose
	Part 2A (Phase 2 portion): Evaluate ORR[a]	42	oral rucaparib, 600 mg BID cycle 1, day 15 and cycle 2+, day 1: pre-dose
	Part 3 (Phase 2 PK portion): Evaluate PK of higher dose strength tablets at 600 mg BID	26	oral rucaparib, 600 mg BID cycle 1, day -7, 1, 15: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 8, 10, 24 hr post-dose or pre-dose cycle 1, day 22, and cycle 2+, day 1: pre-dose
ARIEL2 Phase 2	**Part 1**: Evaluate PFS by HRD subgroup	196	oral rucaparib, 600 mg BID cycle 1, day 15, and cycle 2+, day 1: 12 hr post-dose
	Part 2 (Phase II portion): Evaluate ORR[a] by HRD subgroup	104	oral rucaparib, 600 mg BID cycle 1, day 15, and cycle 2+, day 1: 12 hr post-dose
A4991014 Phase 1	**Dose escalation** Assess safety and tolerability of escalating doses of rucaparib in combination with chemotherapy	Total: 30/35[b]	IV rucaparib: 24, 27, or 40 mg as 30-minute IV infusion oral rucaparib: 72, 80, 120, 180, 240, 360 mg IV & oral: pre-dose, 0.25, 0.5, 1, 1.5, 2.5, 4, 6, 10, 24, and 48 hr after the start of the IV infusion or time of oral dosing

Source: Synopsis of sponsor's population PK report, QS-CLV-006

Results

Rucaparib PK was well described by a two-compartment model with sequential zero-order and first-order absorption and first-order elimination (Figure 3).

Figure 3: Diagram of Rucaparib Model Structure



CL = clearance, Cp = plasma concentration, D1 = duration of the zero-order absorption process, F1 = bioavailability in the central compartment, Ka = absorption rate constant, Vc = volume of the central compartment, Vp = volume of the peripheral compartment.

Source: Sponsor's population PK report, QS-CLV-006

Covariates included in the final population PK model are shown in **Figure 4**.

Figure 4: Diagram of Rucaparib Model Structure

$$LF1_{dose.food,i} = \theta_7 + \begin{cases} \theta_{11}, & \text{fasted/high-fat meal and dose} \leqslant 480 \text{ mg} \\ \theta_{12}, & \text{fasted and dose} > 480 \text{ mg} \\ \theta_{13}, & \text{high-fat meal and dose} > 480 \text{ mg} \end{cases}$$

$$F1_i = {}^{1}/_{(1 + e^{-LF1_i})}$$

$$CL_i = \theta_1 \cdot \left(\frac{\text{BALB}}{40.0}\right)^{\theta_{17}} \cdot \left(\frac{\text{BCLCR}}{82.29}\right)^{\theta_{18}} \cdot \exp(\eta_{CL,i})$$

$$Ka_i = \theta_5 \cdot \left(\frac{\text{DOSE}}{480}\right)^{\theta_{16}} \cdot \left(1 + \theta_{14} \cdot I_{i,\text{fasted}}\right) \cdot \exp(\eta_{Ka,i,*})$$

$$D1_i = \theta_6 \cdot \exp(\eta_{D1,i,*})$$

$$Vc_i = \theta_2$$

$$Q_i = \theta_3$$

$$Vp_i = \theta_4$$

Source: Sponsor's population PK report, QS-CLV-006

- The estimated CL for a typical patient was 10.3 L/hr. The estimates of Vc, Vp, and Q were 16.9 L, 166 L, and 17.4 L/hr, respectively. The typical estimates of F1, Ka, and D1 were 37.2%, 0.0718 hr-1, and 0.619 hr.

- Compared with F1 of 37.2% at all dose levels with a patient selected meal, F1 at doses >480 mg was estimated to be 32.6% and 51.7% under fasted conditions and with a high-fat meal, respectively. At doses ≤480 mg, F1 was 29% under fasted conditions or with a high-fat meal.

- Ka decreased with increasing dose levels. From the starting dose of 600 mg BID to the most reduced dose of 300 mg BID in ARIEL2, the model estimated Ka ranged from 0.0667 to 0.0836 hr-1. Fasted dosing increased Ka by 40%, from 0.0718 hr-1 to 0.100 hr-1, while no apparent effect of a high-fat meal on Ka was observed.

- Increasing baseline CLCR and albumin levels correlated with increasing CL, accounting for approximately 26% and 18% changes in CL, respectively, compared with the typical CL of 10.3 L/hr. Patients with mild and moderate renal impairment showed approximately 15 and 33% higher exposures as compared with patients with normal renal function.

- Concomitant use of proton pump inhibitors (PPIs) moderately increased F1 by 15%. The effect was statistically significant, but unlikely clinically meaningful, and thus not included in the finial PPK model.

- Insufficient data were available for other classes of concomitant drugs, including strong CYP3A4 inhibitors and inducers, and strong BCRP inhibitors.

- Former smokers and patients who never smoked had similar rucaparib exposures. Exposure in current smokers appeared slightly reduced; however, the number of current smokers was low and no meaningful conclusion was made.

- No baseline AAG concentration data were available. Mean or minimum AAG concentration showed no effect on rucaparib disposition.

Parameter estimates and corresponding 95% CI for the final covariate model are summarized in **Table 4**.

Table 4: Parameter Estimates (95% CI) for Rucaparib Final PK Model

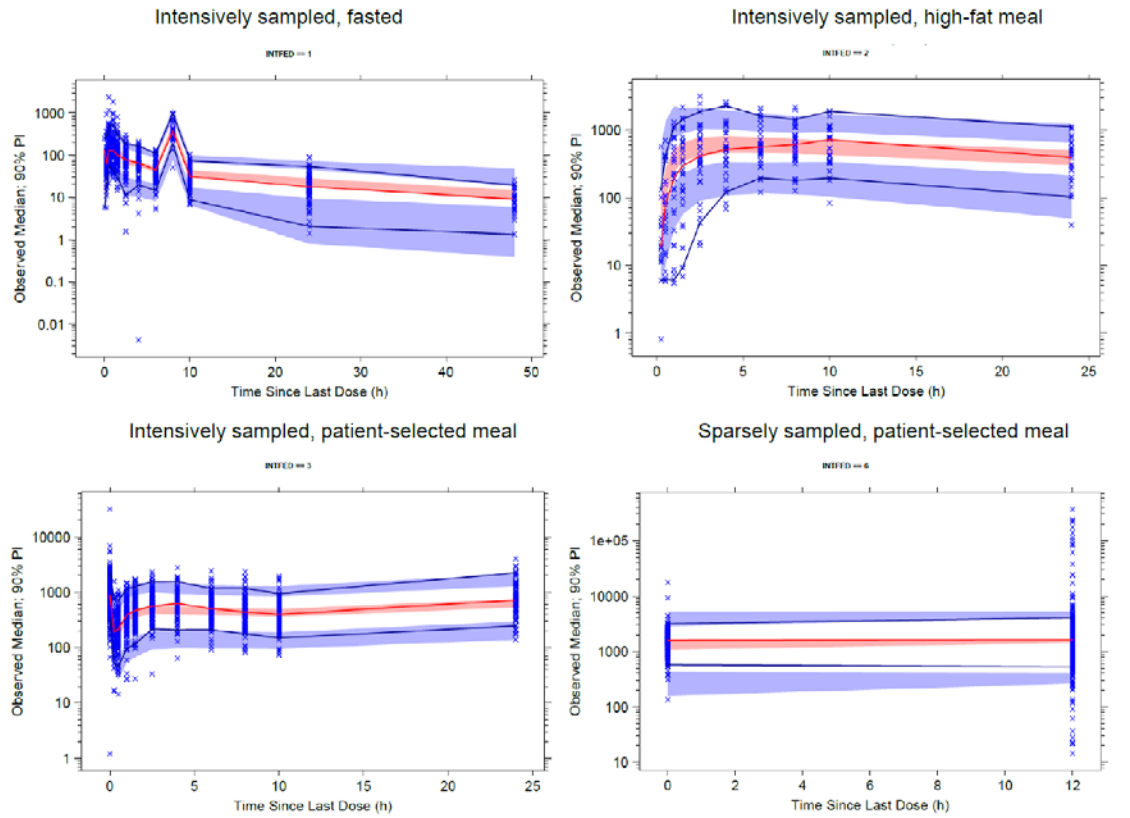
Description	NONMEM Estimate	Bootstrap Estimate	Bootstrap 95% CI	%CV	Shrinkage
θ_1 CL, L/hr	10.26	10.36	(8.573, 12.82)	48.8	8.84
θ_2 Vc, L	16.92	16.98	(13.73, 20.33)	-	-
θ_3 Q, L/hr	17.44	17.9	(14.55, 22.96)	-	-
θ_4 Vp, L	165.9	164.7	(132.5, 199.7)	-	-
θ_5 Ka, hr^{-1}	0.07175	0.0732	(0.05712, 0.0891)	63.5	5.21
θ_6 D1, hr	0.6188	0.6195	(0.4771, 0.812)	111	11.8
θ_7 LF1	-0.5234	-0.5175	(-0.828, -0.1276)	-	-
F1	0.3720	0.3734	(0.3041, 0.4681)	-	-
θ_8 ResErr(Prop), all patients	0.3821	0.3772	(0.3573, 0.3991)	-	-
θ_9 ResErr(Add), intensively sampled patients	0.8314	0.8364	(0.5435, 3.082)	-	-
θ_{10} ResErr(Add), sparsely sampled patients	378.9	377.2	(269.1, 458)	-	-
θ_{11} F1, fasted or a high-fat meal, ≤480 mg	-0.3802	-0.3768	(-0.7392, -0.09048)	-	-
θ_{12} F1, fasted, >480 mg	-0.2017	-0.2686	(-0.7004, 0.1833)	-	-
θ_{13} F1, high-fat, >480 mg	0.5903	0.5518	(0.05534, 1.086)	-	-
θ_{14} Ka, fasted	0.4009	0.4501	(0.1151, 1.072)	-	-
θ_{16} dose on Ka	-0.3249	-0.3012	(-0.4082, -0.1776)	-	-
θ_{17} albumin on CL	0.7202	0.7226	(0.2873, 1.159)	-	-
θ_{18} CLCR on CL	0.3130	0.3213	(0.1969, 0.4463)	-	-
η_1 IIV D1, intensively sampled patients	1.241	1.192	(0.9131, 1.608)	-	-
η_2 IIV KA, intensively sampled patients	0.4035	0.3975	(0.2809, 0.5237)	-	-
η_3 IIV CL, all patients	0.2386	0.2332	(0.1692, 0.3357)	-	-

CL = clearance, CV = coefficient of variation, D1 = duration of the zero-order absorption, F1 = absolute bioavailability, IIV = inter individual variability, LF1 = logit of bioavailability, Ka = absorption rate, Vc = central volume of distribution, Q = inter-compartmental clearance, ResErr(Prop) = proportional residual error, ResErr(Add) = additive residual error, Vp = peripheral volume

Source: Synopsis of sponsor's population PK report, QS-CLV-006

The final model was evaluated by VPC. The VPC was stratified by sampling intensity and food, defining several key populations. **Figure 5** shows pcVPC plots from the final model for intensively sampled data from fasted dosing, intensively sampled and sparsely sampled data from dosing after a patient selected meal, and for intensively sampled data from dosing after a high-fat meal. The model describes the observed data well, and observed data are mostly consistent with the 90% prediction intervals. The pcVPC shows some model misspecification with the lower 95th percentile of observed sparsely sampled troughs falling above the upper end of the 95% prediction interval. The bias could have a minor impact on exposure-response if response is a function of trough concentration.

Figure 5: Prediction-corrected visual predictive check for the final PPK model, stratified by sampling intensity and food



Top left = intensively sampled, fasted; top right = intensively sampled, high-fat meal; bottom left = intensively sampled, patient-selected meal; bottom right = sparsely sampled, patient-selected meal.

Note: The solid red line represents the median of the observed data. The solid blue lines represent the 5th and 95th percentiles of the observed data. The shaded regions encompass 90% of the simulated values (n=500) of the predicted medians (orange), 5th (blue), and 95th (blue) percentiles. Data points (x's) represent the individual observed data.

Source: Sponsor's population PK report, QS-CLV-006

Table 5 provides an overview of the results of the covariate search. The final population PK model was used to predict exposure metrics for a day of dosing at steady-state at each patient's nominal dose. Table 6 provides a summary of the geometric mean and %CV for the model-predicted AUCss, Cmax,ss, and Cmin,ss for all PK evaluable patients with a starting dose of 600 mg BID, and stratified by relevant covariates. For comparison, observed Cmin values at steady-state are also provided. The observed Cmin values are based on trough concentrations in patients with data at least 144 hours after the first dose, and after at least 7 doses of rucaparib. Patients from study A4991014 are not included in the analysis.

Table 5 Overview of the results of the covariate search.

Covariate Tested	PK Parameters Tested				
	Ka	D1	F1	CL	Vc
Food	S	unclear	S		
Dose	S	NS	S		
Body weight (kg) or BMI (kg/m2)	NS	NS	NS	NS	NS
Age (yrs)	NS	NS	NS	NS	NS
Race	NS	NS	NS	NS	NS
Baseline creatinine clearance				S	
Baseline liver enzymes[a] (ALT, AST, bilirubin)				NS	
AAG[b]				ID	ID
Baseline albumin				S	NS
CYP1A2 inhibitor – concomitant				NS	
CYP2D6 inhibitor – concomitant				NS	
CYP3A4 inhibitor – concomitant[c]				ID	
CYP3A4 inducer – concomitant[c]				ID	
P-gp inhibitor – concomitant	NS		NS	NS	
BCRP inhibitor – concomitant[c]	ID		ID	ID	
PPI – concomitant	NS	NS	S		
Covariate Tested	**PK Parameters Tested**				
	Ka	**D1**	**F1**	**CL**	**Vc**
CYP1A2[b], CYP2D6[b] phenotype				ID	
Smoking Status (CYP1A2 induction)				NS	
BRCA mutation[b]	ID	ID	ID	ID	ID
BRCA status[b]	ID	ID	ID	ID	ID

AAG = alpha-1 acid glycoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCRP = breast cancer resistance protein, CL = clearance, CYP = cytochrome P450, F1 = bioavailability, ID = not tested due to insufficient data, NS = not significant, P-gp = p-glycoprotein, PK = pharmacokinetic, PPI = proton-pump inhibitor, S = significant, Vc = central volume of distribution
BRCA mutations: BRCA1 vs. BRCA2 vs. BRCA wild type/unknown.
BRCA status: germline BRCA mutation vs. t somatic BRCA mutation vs. BRCA mutation, germline/somatic status not determined vs. BRCA wild type/unknown

[a] Evaluated as separate effects.
[b] Insufficient data for covariate testing in PPK model. Covariate tested by comparing post hoc estimates of steady-state exposures and observed C_{min} at 600 mg BID, and by comparing post hoc estimates of CL at all doses, where appropriate.
[c] Insufficient data for testing in the model or for comparing post hoc PK exposures or parameter estimates.

Source: Sponsor's population PK report, QS-CLV-006

Table 6 Summary of predicted and observed steady-state exposures for 600 mg BID.

Population	Predicted AUC_{ss} (ng.hr/mL)	Predicted $C_{max,ss}$ (ng/mL)	Predicted $C_{min,ss}$ (ng/mL)	Observed $C_{min,ss}$ (ng/mL)
All patients	44373 (42%) N=372	2041.4 (39%) N=372	1619.1 (45%) N=372	1559.9 (86%) N=359
Tablet Strength[a]				
40/60 mg	39307 (46%) N=34	1830.2 (43%) N=34	1415.9 (49%) N=34	1525.6 (66%) N=34
120 mg	44720 (37%) N=211	2050.8 (34%) N=211	1636.9 (41%) N=211	1592.4 (95%) N=207
200/300 mg	45247 (47%) N=127	2085.9 (45%) N=127	1648.1 (50%) N=127	1514 (76%) N=118
Renal Impairment Category				
Normal (>60 mL/min)	42492 (40%) N=296	1959.9 (38%) N=296	1545.5 (43%) N=296	1505.1 (86%) N=287
Mild (>40 to 59 mL/min)	52079 (42%) N=71	2374.4 (39%) N=71	1922.2 (46%) N=71	1764.2 (86%) N=67
Moderate (>20 to 39 mL/min)	59258 (39%) N=5	2667.4 (36%) N=5	2221.9 (42%) N=5	2331.9 (53%) N=5
Hepatic Impairment Category[b]				
Normal	44794 (41%) N=337	2060.9 (39%) N=337	1634.3 (45%) N=337	1605.6 (79%) N=327
Mild	40646 (45%) N=34	1868.3 (43%) N=34	1484.9 (48%) N=34	1146.9 (150%) N=31
Moderate	36367 (NA) N=1	1689.6 (NA) N=1	1308.6 (NA) N=1	1710 (NA) N=1
Smoking Status				
Missing	41965 (37%) N=2	1931.1 (34%) N=2	1529.1 (41%) N=2	1647.2 (56%) N=2
Current smoker	34011 (57%) N=16	1599.5 (54%) N=16	1206.8 (61%) N=16	1109.3 (76%) N=16
Former smoker	44530 (41%) N=97	2048.7 (39%) N=97	1625.6 (44%) N=97	1587 (69%) N=95
Never smoker	45073 (40%) N=257	2070.8 (38%) N=257	1647.3 (44%) N=257	1583.5 (93%) N=246
Concomitant PPI				
no concomitant PPI	43153 (41%) N=245	1986.9 (39%) N=245	1572.9 (45%) N=245	1502.8 (94%) N=235
with concomitant PPI	46824 (42%) N=127	2150.9 (39%) N=127	1712.2 (45%) N=127	1674 (70%) N=124
Concomitant PGP inhibitor				
no concomitant PGP inhibitor	44419 (41%) N=345	2041.7 (38%) N=345	1622.3 (44%) N=345	1576 (86%) N=334
with concomitant PGP inhibitor	43790 (51%) N=27	2037.1 (48%) N=27	1578.9 (56%) N=27	1359.7 (87%) N=25
Concomitant CYP1A2 Inhibitor				
no concomitant CYP1A2 inhibitor	44036 (41%) N=353	2026.2 (38%) N=353	1606.4 (44%) N=353	1560.4 (84%) N=340
with concomitant CYP1A2 inhibitor	51120 (55%) N=19	2346.1 (52%) N=19	1874.9 (60%) N=19	1550.5 (130%) N=19
Concomitant CYP2D6 inhibitor				
no concomitant CYP2D6 inhibitor	44375 (41%) N=350	2040.8 (38%) N=350	1619.7 (44%) N=350	1568.2 (86%) N=337
with concomitant CYP2D6 inhibitor	44334 (52%) N=22	2050.9 (52%) N=22	1609.8 (54%) N=22	1437 (86%) N=22

Population	Predicted AUC_{ss} (ng.hr/mL)	Predicted $C_{max,ss}$ (ng/mL)	Predicted $C_{min,ss}$ (ng/mL)	Observed $C_{min,ss}$ (ng/mL)
BRCA status				
Germline BRCA mutation	43856 (48%) N=111	2027.4 (46%) N=111	1593 (52%) N=111	1466.9 (110%) N=108
Somatic BRCA mutation	40800 (42%) N=23	1883.9 (39%) N=23	1480.7 (46%) N=23	1304.9 (140%) N=23
BRCA mutation, germline/somatic status not determined	42444 (58%) N=18	1962.1 (56%) N=18	1542.3 (61%) N=18	1512.7 (54%) N=17
BRCA wild type/ unknown	45193 (37%) N=220	2072.5 (34%) N=220	1654.3 (40%) N=220	1645.4 (71%) N=211
BRCA mutation				
BRCA1	44063 (42%) N=89	2029.8 (39%) N=89	1604.9 (46%) N=89	1400.8 (130%) N=88
BRCA2	42038 (57%) N=63	1952.2 (55%) N=63	1520.7 (60%) N=63	1513.8 (72%) N=60
BRCA wild/ unknown	45193 (37%) N=220	2072.5 (34%) N=220	1654.3 (40%) N=220	1645.4 (71%) N=211
Gender				
Male	19816 (49%) N=5	952.3 (51%) N=5	689.54 (48%) N=5	569.49 (49%) N=4
Female	44863 (40%) N=367	2062.7 (38%) N=367	1638 (44%) N=367	1577.7 (85%) N=355
Race				
White	44267 (42%) N=298	2036.4 (39%) N=298	1615.7 (45%) N=298	1619.7 (71%) N=287
Asian	44605 (39%) N=22	2047.9 (36%) N=22	1630.6 (42%) N=22	843.25 (350%) N=21
Black	61447 (28%) N=8	2774.3 (27%) N=8	2292.4 (29%) N=8	2437.4 (41%) N=8
American Indian/ Alaska Native	51471 (NA) N=1	2332.9 (NA) N=1	1911.9 (NA) N=1	2520 (NA) N=1
other	42205 (43%) N=43	1952.2 (40%) N=43	1528.3 (47%) N=43	1489.7 (72%) N=42
CYP1A2 Phenotype				
Normal	43513 (37%) N=28	1998.9 (35%) N=28	1589.2 (41%) N=28	1503.4 (110%) N=28
Hyperinducer	43246 (37%) N=136	1987.9 (35%) N=136	1578.2 (41%) N=136	1691.2 (61%) N=133
Not collected	45244 (45%) N=208	2083 (42%) N=208	1650.6 (48%) N=208	1485.2 (98%) N=198
CYP2D6 Phenotype				
Poor	39219 (37%) N=9	1815.1 (34%) N=9	1418.9 (41%) N=9	1603.2 (41%) N=9
Normal	42831 (35%) N=76	1969.6 (33%) N=76	1562.2 (39%) N=76	1686.1 (58%) N=75
Intermediate	44741 (41%) N=71	2052.6 (38%) N=71	1637.1 (45%) N=71	1720.2 (63%) N=69
Ultra-rapid	36840 (32%) N=4	1711.7 (29%) N=4	1326.1 (35%) N=4	1633.3 (62%) N=4
Not collected	45209 (44%) N=212	2081.2 (42%) N=212	1649.3 (48%) N=212	1462.5 (100%) N=202

Note: AUC_{ss} = area under the concentration time curve at steady state, BID = twice a day, $C_{max,ss}$ = maximum plasma concentration at steady state, $C_{min,ss}$ = minimum plasma concentration at steady state, CV = coefficient of variation,

Source: Sponsor's population PK report, QS-CLV-006

Reviewer's comments:

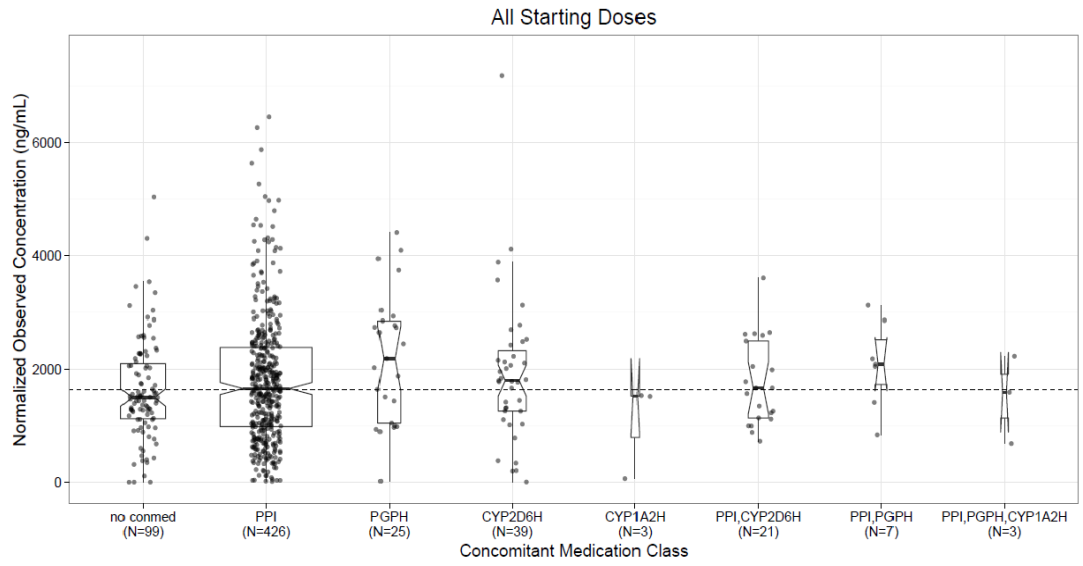
- *From the population PK perspective, the reviewer agrees with sponsor's conclusion that no significant on effect on PK was identified for age, race, baseline body mass index, and hepatic functions.*

Concomitant Medication Evaluation by PPK analysis

FDA reviewer sent out an information request asking sponsor to evaluate the DDI by treatment concomitant drug as time dependent variables (Appendix). Based on sponsor's response to this IR, concomitant strong CYP1A4, CYP2D6, p-gp inhibitor and PPI were evaluated.

Sponsor pointed out that the patients taking strong CYP2D6 inhibitors, CYP1A2 inhibitors, and P-gp inhibitors were too few (i.e., at least 30 patients) to reliably detect a DDI effect via PPK analysis [1]. Instead, trough observations stratified by concomitant medication were plotted (**Figure 6**).

Figure 6: Boxplots of Trough Observations Stratified by Concomitant Medication



Note: Data from all nominal dose groups are included. N's reported below each boxplot indicate the number of observations. Steady-state trough observations are stratified by concomitant medication. Observations associated with multiple medications are labelled as such. Observations are dose-normalized to 600 mg based on the actual dose. Notches in each boxplot are used to compare groups. Figure includes patients of all starting doses with steady-state trough concentrations and patient-selected meal.

SS, steady-state; PPI, proton-pump inhibitor; PGPH, P-glycoprotein inhibitor; CYP2D6H, CYP2D6 inhibitor; CYP1A2H, CYP1A2 inhibitor

Source: QS-CLV-006 Addendum 1, Appendix 1.5.1

The PPI effects on D1 and F1 were evaluated in the final PPK model. Inclusion of time-varying PPI covariate effects on D1 and F1 were tested the final PPK model. The addition of the effect of PPI on D1 did not result in a statistically significant improvement in the final PPK model. The addition of the PPI effect on F1 to the final model did result in a statistically significant improvement in the final model fit ($p<0.05$) as judged by the change in objective function value; however, the parameter was poorly estimated (208% RSE). In the previous analysis and in the current analysis, rucaparib bioavailability with concomitant PPI as a time-independent covariate estimated increases in F1 of 15% and 16%, respectively, over treatment without concomitant PPI. When estimating the PPI effect using a time-varying PPI effect, the estimate of F1 was 10.5% lower (34%) than the typical estimate of F1 without PPI (38%). The estimated effect was unlikely clinically meaningful (<20%).

Reviewer's comments:

Sponsor's analysis seems reasonable. The concomitant PPI is unlikely to have clinically meaningful impact upon rucaparib PK. Data were not sufficient to evaluate the DDI for concomitant strong CYP1A4, CYP2D6, and p-gp inhibitor.

10.4.4. Pharmacometrics Exposure-Response Analysis

10.4.4.1. Sponsor's Exposure-Response Analysis

In the QS-CLV-007 and addendum, sponsor conducted exposure response analysis to:

- Evaluate the relationship between exposures and the incidence/severity of selected safety endpoints
- Evaluate the relationship between exposures and selected efficacy endpoints
- Evaluate covariates that affect the safety and efficacy of rucaparib
- Provide supplemental evidence to the integrated summary of safety (ISS) and integrated summary of efficacy (ISE) to support the 600 mg BID regimen.

Exposure-efficacy Analysis

Data

Variable	Study 10 Part 1	Study 10 Part 2A	ARIEL2 Part 1	ARIEL2 Part 2	All
N	15	42	24	40	121
N PK	15	39	24	39	117
$C_{min,ss}$ (ng/mL)	1266 (1038) [69,3258]	1860 (907) [656,6135]	1585 (641) [844,3143]	1691 (788) [599,3775]	1671 (848) [69,6135]
$C_{max,ss}$ (ng/mL)	1806 (1401) [174,4461]	2266 (944) [952,6638]	1977 (678) [1173,3607]	2091 (841) [884,4369]	2089 (936) [174,6638]
AUC_{ss} (ng/ml*hr)	36697 (29108) [2450,92039]	49992 (22346) [19441,154166]	43168 (15963) [24434,81711]	45838 (19717) [17902,98539]	45503 (21487) [2450,154166]
Average/Nominal Dose Ratio	1.12 (0.59) [0.46,2.66]	0.75 (0.15) [0.42,1]	0.89 (0.13) [0.48,1.02]	0.86 (0.17) [0.45,1.11]	0.86 (0.27) [0.42,2.66]
$C_{min,avg,ss}$ (ng/mL)	1102 (793) [65,2446]	1315 (468) [603,2576]	1403 (605) [600,3206]	1472 (806) [390,3812]	1358 (668) [65,3812]
$C_{min,obs,ss}$ (ng/mL)	1740 (1392) [66,3710]	2035 (1434) [8,7930]	1780 (1032) [573,4900]	2140 (1491) [410,8140]	1982 (1368) [8,8140]
$C_{max,avg,ss}$ (ng/mL)	1632 (1086) [166,3745]	1614 (494) [876,2999]	1751 (650) [817,3679]	1817 (886) [540,4413]	1712 (756) [166,4413]
$AUC_{avg,ss}$ (ng/ml*hr)	32613 (22359) [2328,73569]	35500 (11616) [17886,67373]	38242 (15179) [17171,83345]	39857 (20469) [11271,99524]	37145 (17140) [2328,99524]

Note: Continuous variables are reported as mean (SD), [min, max]. AUC refers to daily 0-24 hr AUC.
Acronyms: $AUC_{avg,ss}$ = average steady-state AUC, AUC_{ss} = steady-state AUC, $C_{max,ss}$ = steady-state C_{max}, $C_{max,avg,ss}$ = average steady-state C_{max}, $C_{min,ss}$ = steady-state C_{min}, $C_{min,avg,ss}$ = average steady-state C_{min}, $C_{min,obs,ss}$ = observed steady-state C_{min}

Exposure-ORR analysis

Sponsor explored exposure-ORR relationship by adapting exposure metrics derived before confirmed response or progressive disease, as instructed by FDA, in order to generate a less biased estimate due to dose modification. The exposure metrics (AUCavg,ss*) was calculated using the following equations:

$$AUC_{avg,ss*} = \text{Post hoc steady state AUC at the nominal starting dose} \times \text{Average dose ratio, and}$$

$$\text{Average dose ratio} = \frac{\text{Cumulative dose up until event of interest} \times \text{Dosing duration until event of interest}}{\text{Nominal starting dose}},$$

Objective response rate evaluated by IRR was used as the efficacy endpoint. Multiple model structures including linear and nonlinear model were evaluated. Specifically, log-linear and Emax and sigmoid Emax models as follows were considered:

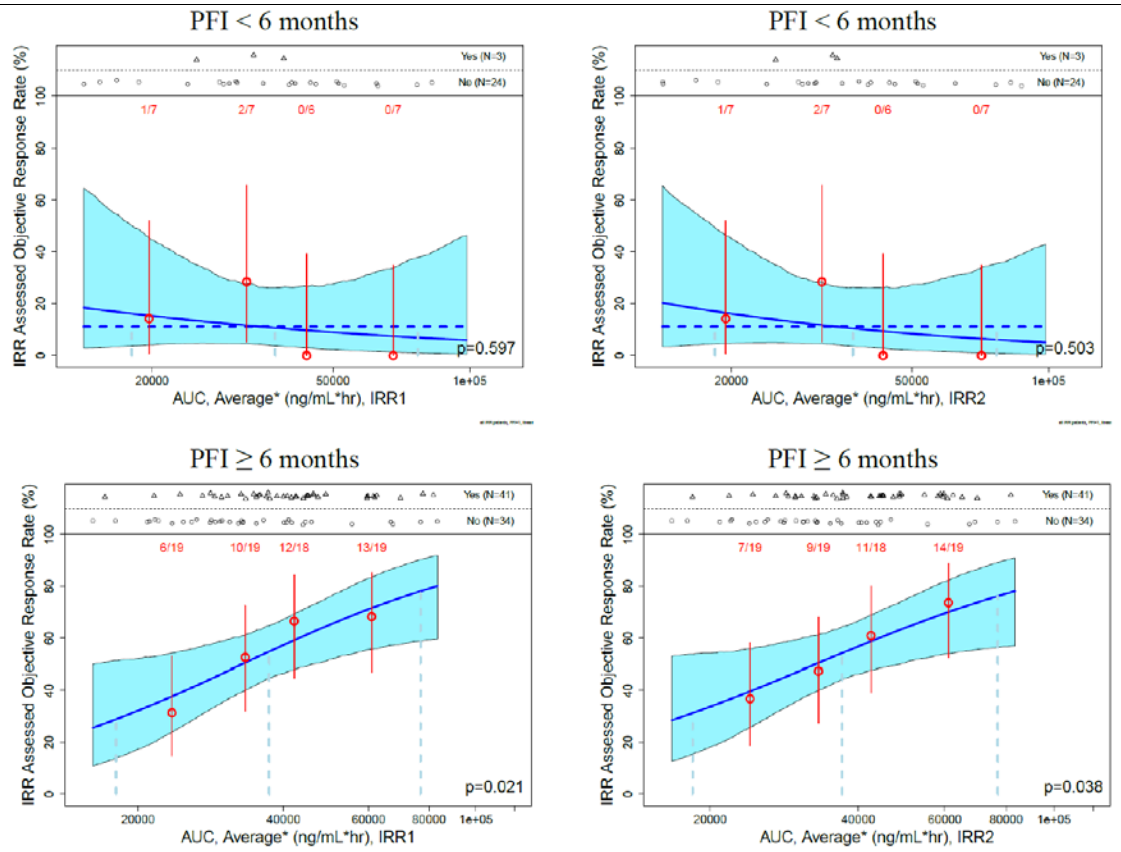
log-linear: $\Pr(\text{Response}) = \text{invlogit}(\text{Intercept} + \text{Slope} \times \ln(\text{Exposure}) + \text{Covariate Effects})$

Emax (γ=1) or sigmoid Emax: $\Pr(\text{Response}) = \text{invlogit}(\text{Intercept} + \text{Emax} \times \text{Exposure}^{\gamma}/(\text{Exposure}^{\gamma} + \exp(\text{EC50})^{\gamma}) + \text{Covariate Effects})$

Sponsor's results showed that no statistically significant exposure-response relationship was detected for the IRR and investigator assessed RECIST response in the logistic regression analysis (Figure 7), but the data suggest a trend of increasing response rate as assessed by IRR with increasing rucaparib exposure.

Additional evaluation of IRR assessed response was performed where the effect of PFI category was examined in more detail for this endpoint. In the lowest PFI category (< 6 months), the observed response rate was 11% (3 responses in 27 patients), while the response rates in the 6-12 months and ≥ 12 months categories were 54% (28/52) and 57% (13/23), respectively. No patients in the IRR population were missing PFI. The exploratory graphics in Figure 4 show the exposure-response relationships in patients with PFI <6 months and in patients with PFI ≥ 6 months, with separate linear regressions.

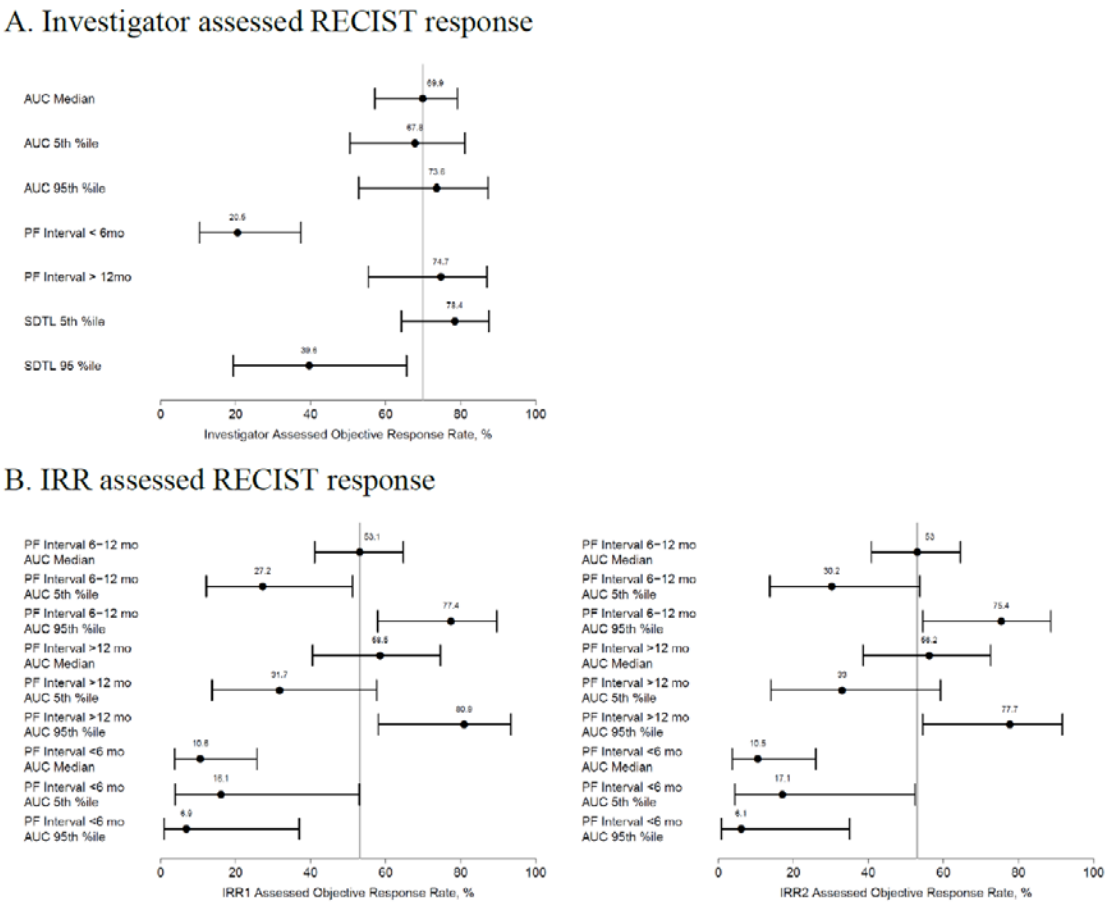
Figure 7: Exposure-response relationships for IRR assessed RECIST response in patients with PFI < or ≥ 6 months



Source: Addendum 3 of sponsor's Exposure-Response Report, QS-CLV-007

Analysis was performed to evaluate covariates for ORR. The effects of exposure and significant covariates on efficacy endpoints were shown in Figure 8.

Figure 8: Forest plots showing effects of efficacy covariates



Note: The vertical line of each forest plot represents the response rate in the exposure-efficacy patient with nominal characteristics: median AUCavg,ss* (different for each endpoint), age<65-yrs, white, germline BRCA1 mutation, two prior chemotherapies, progression-free interval of 6-12 months, and baseline sum of diameters of target lesions of 55 mm. The solid points represent estimated response rates in other populations; with horizontal bars indicate 5th to 95th percentile confidence intervals.

Source: Addendum of sponsor's Exposure-Response Report, QS-CLV-007

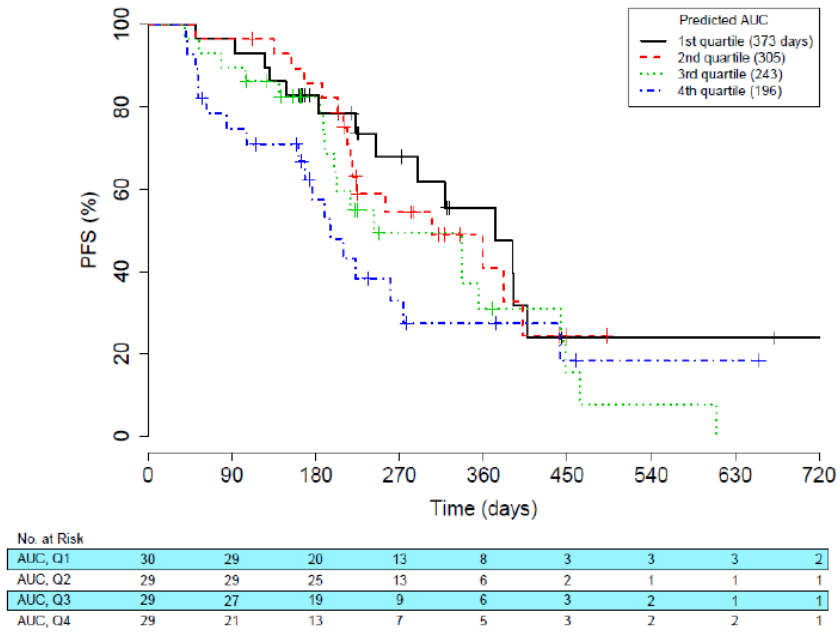
Reviewer's comment: The exposure metrics were calculated by multiplying the individual post-hoc steady-state exposure metrics at the nominal dose by the average dose ratio that was calculated as the cumulative dose up until the relevant event / dosing duration until the relevant event / starting dose. This exposure metrics is more pertinent to estimate the E-R relationship between rucaparib exposure and confirmed ORR. It also reduces the bias derived from dose adjustment. However, this exposure metrics used in the exposure-ORR analysis might still not able to fully address the dose-adjustment caused E-R estimation bias. The time to the relevant events in non-responders (SD+PD) is longer than the responders (see Appendix 4.2), which might have greater chance to experience more dose reductions as compared with responders.

Exposure-PFS analysis

Sponsor explored exposure-PFS relationship by generating exploratory Kaplan-Meier (KM) plots for different quantiles of rucaparib exposure and developing PH survival models.

The exploratory KM plot for PFS is shown in Figure 9. The plot shows no clear difference between the different quartiles of rucaparib exposure and the time to progressive disease or death. Exposure were calculated by multiplying the steady-state PK parameters by the average dose ratio, which was calculated for each patient as total cumulative dose (mg)/whole dosing duration (day)/nominal dose (mg/day). And the AUCavg,ss was utilized for exposure-PFS analysis.

Figure 9: Kaplan-Meier Plots for PFS by Exposure Quartiles



Note: This figure shows Kaplan-Meier curves stratified by exposure quartile. The median survival time per quartile is indicated in the legend. The number of patients per quartile still surviving is indicated in the horizontal rows underneath the plot.

Source: Synopsis of Exposure-Response Report, Study No. QS-CLV-007

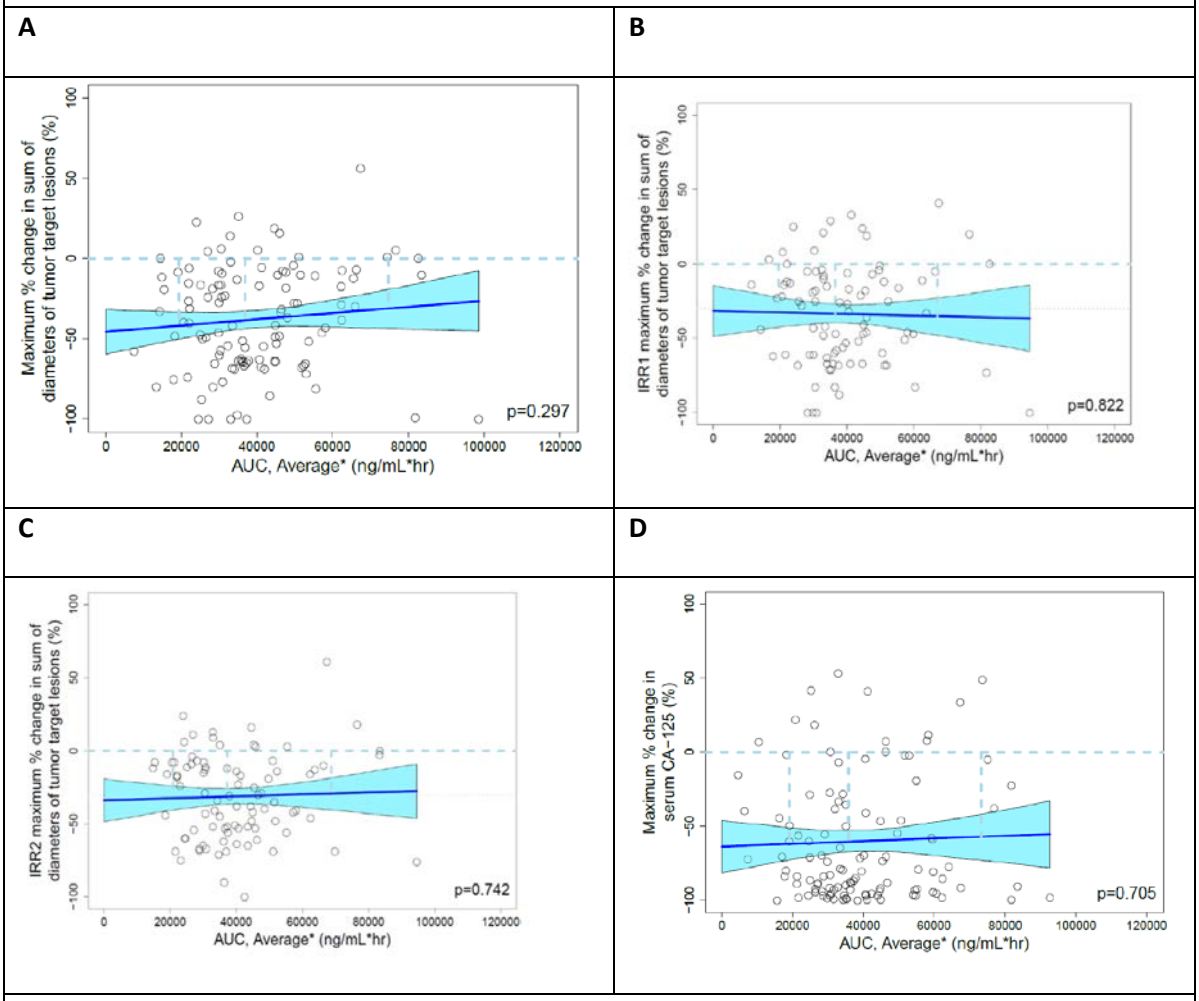
Reviewer's comment: The result from exploratory KM plot for exposure-PFS analysis is biased. Due to the dose reduction/interruption in the trial, the exposure showed a downward trend in a general manner and subjects who had longer time to progressive disease or death could have higher chance to experience dose interruption/reduction. Thus, the AUCavg,ss tends to be lower in the patients with longer PFS, which made the exposure-PFS relationship look flat. Indeed, sponsor's E-R for PFS analysis showed a

"reversed" E-R relationship. To incorporate the dose-modification in the E-R analysis, the time-varying PK metrics should be used. See section 3 for details.

Other Exposure-Efficacy Analysis

The left panel in Figure 10 shows the exposure-response relationship for the maximum percent change from baseline in the sum of diameters of tumor target lesions (per RECIST v1.1). The right panel in Figure 10 shows the exposure-response relationship for the maximum percent change from baseline in serum CA-125. No significant exposure-response relationships or trends were detected.

Figure 10: Exposure-response relationship for the maximum % change in the sum of diameters of tumor target lesions (A-C)and serum CA-125 (D)



Source: Addendum of sponsor's Exposure-Response Report, QS-CLV-007 and response to IR-20161028a

Exposure-Safety Analysis

Data

Table 7 Exposure summary in the exposure-safety analysis patients

Variable	Study 10 Part 1	Study 10 Part 2A	Study 10 Part 3	ARIEL2 Part 1	ARIEL2 Part 2	All
N	20	42	16	204	111	393
N PK	20	39	16	196	104	375
$C_{min,ss}$ (ng/mL)	1451 (1308) [12,4407]	1860 (907) [656,6135]	2068 (1396) [670,5910]	1707 (676) [638,3883]	1813 (735) [599,4134]	1754 (805) [12,6135]
$C_{max,ss}$ (ng/mL)	1974 (1663) [82,5754]	2266 (944) [952,6638]	2565 (1651) [1016,7045]	2106 (716) [932,4362]	2229 (788) [884,4736]	2169 (890) [82,7045]
AUC_{ss} (ng/ml*hr)	40918 (35510) [750,120794]	49992 (22346) [19441,154166]	55929 (36677) [20404,156920]	46210 (16844) [18978,99712]	48992 (18424) [17902,107289]	47507 (20436) [750,156920]
Average/Nominal Dose Ratio	1.02 (0.55) [0.26,2.66]	0.75 (0.15) [0.42,1]	0.65 (0.28) [0.07,0.94]	0.91 (0.15) [0.21,1.86]	0.88 (0.15) [0.45,1.26]	0.88 (0.21) [0.07,2.66]
$C_{min,avg,ss}$ (ng/mL)	1113 (904) [11,3129]	1315 (468) [603,2576]	1150 (716) [116,3014]	1520 (605) [317,5403]	1589 (707) [390,3812]	1480 (657) [11,5403]
$C_{min,obs,ss}$ (ng/mL)	1623 (1468) [25,4370]	2035 (1434) [8,7930]	1689 (1053) [261,4530]	2024 (1144) [22,6260]	2131 (1438) [397,8140]	2022 (1277) [8,8140]
$C_{max,avg,ss}$ (ng/mL)	1589 (1201) [75,4086]	1614 (494) [876,2999]	1438 (833) [134,3593]	1881 (654) [400,6254]	1954 (778) [540,4413]	1839 (732) [75,6254]
$AUC_{avg,ss}$ (ng/ml*hr)	32205 (25087) [690,85764]	35500 (11616) [17886,67373]	31239 (18589) [3028,80029]	41231 (15235) [8697,141157]	42934 (17955) [11271,99524]	40200 (16767) [690,141157]

Note: Continuous variables are reported as mean (SD), [min, max]. AUC refers to daily 0-24 hr AUC.
Acronyms: $AUC_{avg,ss}$ = averaged steady-state AUC, AUC_{ss} = steady-state AUC, $C_{max,ss}$ = steady-state C_{max}, $C_{max,avg,ss}$ = averaged steady-state C_{max}, $C_{min,ss}$ = steady-state C_{min}, $C_{min,avg,ss}$ = averaged steady-state C_{min},

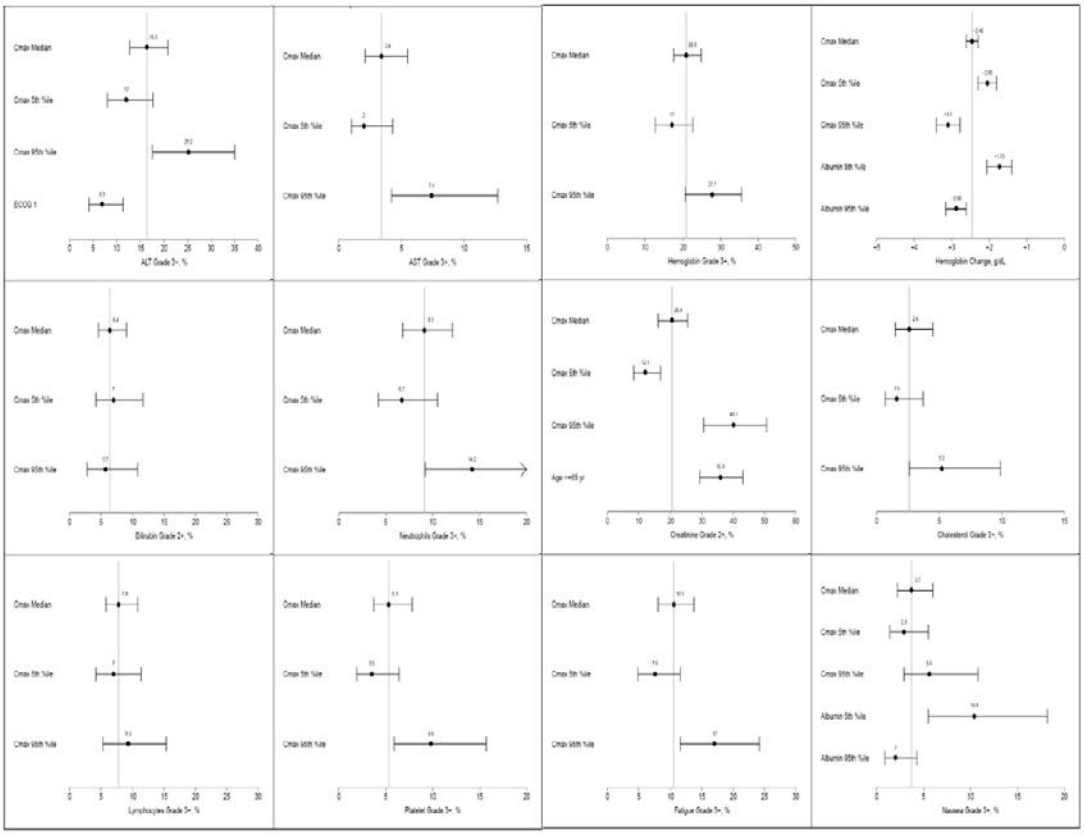
Source: Sponsor's Exposure-Response Report, Study No. QS-CLV-007

Exposure-safety relationships

In total, exposure-safety analysis was conducted with data from 393 ovarian cancer patients. Daily Cmax was selected as the exposure metric, and individual Cmax values were calculated from a population PK analysis. The dose-averaged steady-state Cmax was used as the exposure measure. Statistically significant exposure-response relationships ($p<0.05$) were observed for Grade ≥2 creatinine, Grade ≥3 ALT, Grade ≥3 AST, Grade ≥3 fatigue/asthenia, and Grade ≥3 platelets. Following 600 mg rucaparib BID, the model-projected incidences were 30.1% for Grade ≥2 creatinine, 10-20% for Grade ≥3 ALT and Grade ≥3 fatigue/asthenia, and <10% for Grade ≥3 platelets and Grade ≥3 AST. The model-estimated mean hemoglobin decrease from baseline was 2.5 g/dL. No statistically significant exposure-response relationship was identified for Grade ≥2 bilirubin, Grade ≥3 neutrophils, Grade ≥3 lymphocytes, Grade ≥ 3 hemoglobin, Grade ≥3 cholesterol, and Grade ≥3 nausea.

Effects of covariates on the safety endpoints were evaluated in multivariate models. Although statistically significant correlations were identified for some covariates, the clinical significance and predictive value of these covariates have not been established. The forest plot for exposure-safety analysis is shown in Figure 11.

Figure 11: Forest plots showing effects of safety covariates



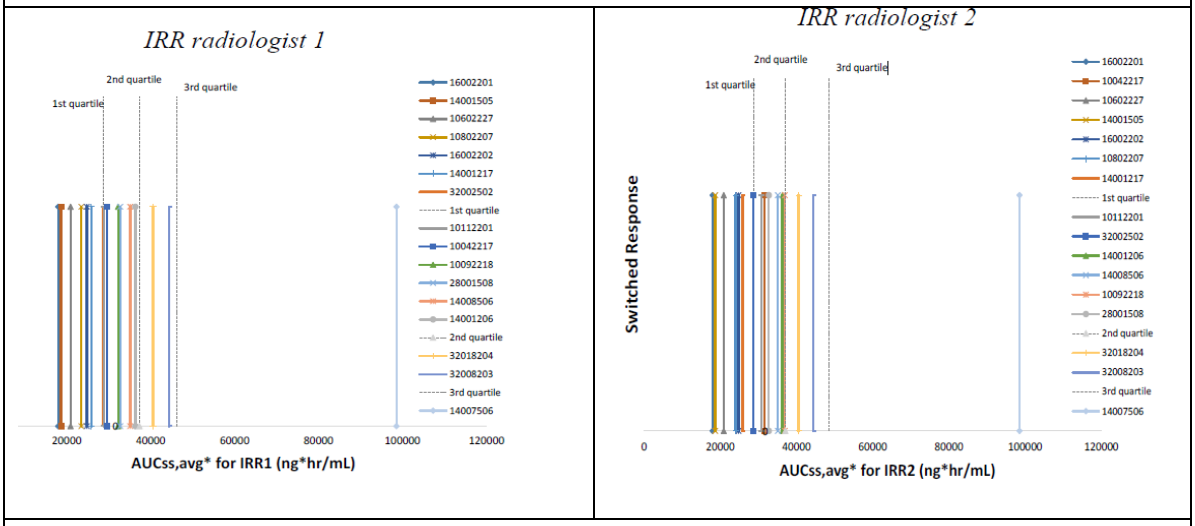
Note: The vertical line of each forest plot represents the response rate in the patient with nominal characteristics: Cmax,avg,ss = 1774 ng/mL, age < 65-yrs, white, germline BRCA mutation (by GSA), two prior chemotherapies, baseline ECOG of 0, and baseline albumin of 41 g/dL. The solid points represent estimated response rates in other populations, with horizontal bars indicate 5th to 95th percentile confidence intervals.

Source: Sponsor's Exposure-Response Report, QS-CLV-007

Comparison of E-R analysis between IRR and investigator assessed response

In the E-R analysis for confirmed ORR, it seems that the slope between rucaparib exposure and ORR is steeper in the IRR assessed ORR as compared with investigator assessed ORR. There were 16 patients who were responders by INV but not IRR assessment (as listed IR-21061012a provided by FDA). Responses and corresponding AUCavg,ss* by IRR assessment for the 16 patients are plotted in Figure 12, with each solid line representing a patient. In the previous analysis (left panel), most patients (13/16) have AUCavg,ss* in the first (7/16) or second (6/16) quartile as compared to the 102 patients in the overall data set. Thus there are more non-responders with lower exposures in the IRR ER analysis as compared to the INV ER analysis, which accounts for the observed differences in the ER relationships.

Figure 12: Responses and corresponding AUCavg,ss* by IRR assessment for the patients who had response assessed by investigator but not IRR



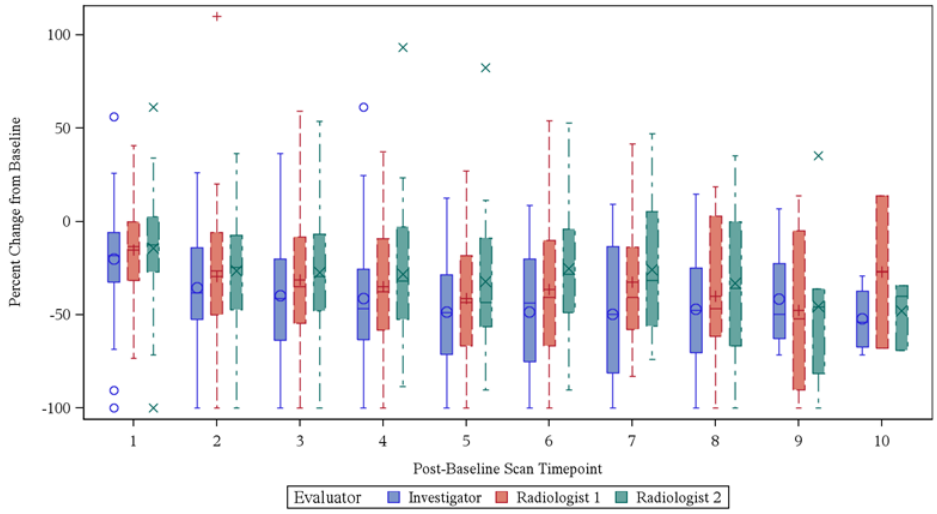
Note: In the legend, patient numbers are sorted by AUCavg,ss*. Solid vertical lines represent the 16 patients who were INV responders but IRR non-responders. Quartiles are shown as grey dashed lines based on AUCavg,ss* data for the 102 patients who had both investigator and IRR response data.

Source: Sponsor's response to FDA IR-20161028a

In addition, the longitudinal sum of target lesions was compared between investigator and IRR assessment. Although the tumor percent change from baseline are overlapping between the investigator and the two independent radiologists over time, it seems IRR assessed tumor dynamics showed smaller reduction of tumor size and this kind of difference seems more significant for patients with exposures in Q1 and Q2 (Figure 13).

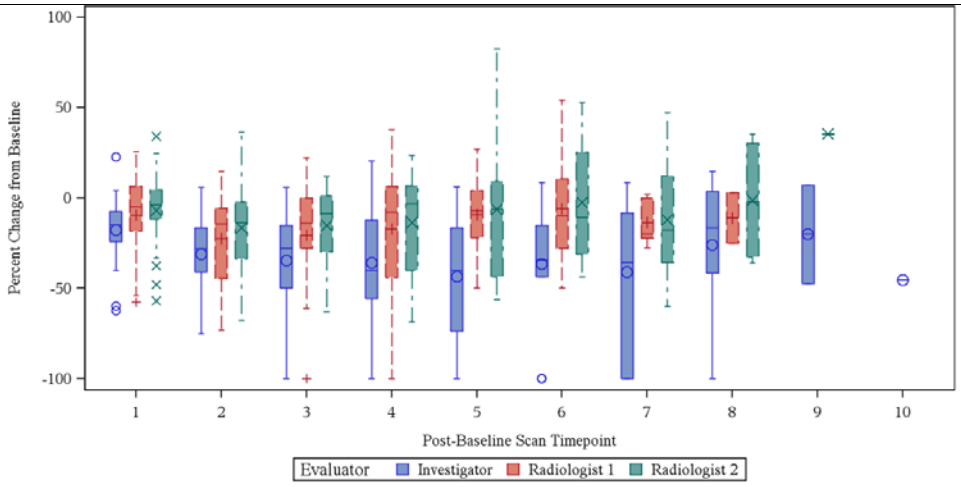
Figure 13: Box Plot of Percent Change in the Sum of Diameters of Target Lesions for Investigator Assessment, Independent Radiologist 1, and Independent Radiologist 2 for All patients (A), the Lowest Exposure Quartile (Q1, B) and Second to Lowest Exposure Quartile (Q2, C)

A



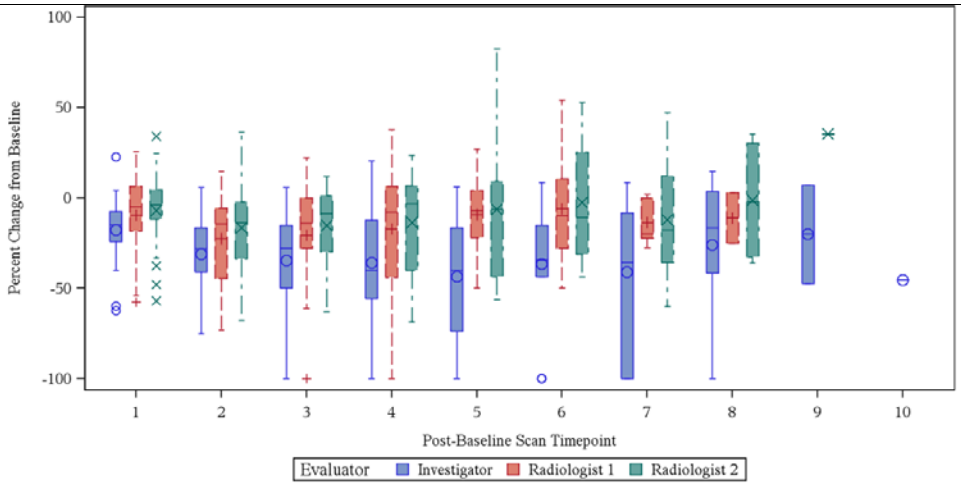
Note: Includes only patients who have a baseline and postbaseline value, per evaluator.

B



*Average steady-state AUC up until the relevant event for each evaluator.
Note: Includes only patients who have a baseline and postbaseline value, per evaluator.

C



*Average steady-state AUC up until the relevant event for each evaluator.
Note: Includes only patients who have a baseline and postbaseline value, per evaluator.

Note: In the legend, patient numbers are sorted by AUCavg,ss*. Solid vertical lines represent the 16 patients who were INV responders but IRR non-responders. Quartiles are shown as grey dashed lines based on AUCavg,ss* data for the 102 patients who had both investigator and IRR response data.

Source: Sponsor's response to FDA IR-20161028a

10.4.4.2. Reviewer's Exposure-Response Analysis

Introduction

The reviewer initiated an independent analysis to investigate the exposure-PFS relationship taking dose-adjustment into account.

Objectives

Analysis objectives are:

- Develop a longitudinal exposure - PFS model to evaluate if the relative risk of PFS to the proposed 600 mg BID dose would increase with lower drug exposure

Data Sets

Data set are summarized in the following table:

Study #	Name	Link to EDR
CO-338-010, CO-338-017	effer.xpt	\\cdsesub1\evsprod\nda209115\0002\m5\datasets\qs-clv-007\analysis\legacy\datasets\effer.xpt
CO-338-010	ador.xpt	\\cdsesub1\evsprod\nda209115\0002\m5\datasets\co-338-010\analysis\adam\datasets\ador.xpt
CO-338-017	ador.xpt	\\cdsesub1\evsprod\nda209115\0002\m5\datasets\co-338-017\analysis\adam\datasets\ador.xpt
A4991014, CO-338-010, CO-338-017	nmruc-stud1014-10-17-15apr16-csv.xpt	\\cdsesub1\evsprod\nda209115\0002\m5\datasets\qs-clv-006\analysis\legacy\datasets\nmruc-stud1014-10-17-15apr16-csv.xpt
CO-338-010, CO-338-017	effer-ir20161018b.xpt	\\cdsesub1\evsprod\nda209115\0035\m5\datasets\qs-clv-007\analysis\legacy\datasets\effer-ir20161018b.xpt

Software

NONMEM version 7.3 was used for all the simulations. R version 3.3.0 was used for data handling, visualization, and post-processing.

Results and Discussions

Exposure-PFS analysis

FDA reviewer developed Cox PH models to evaluate the relationship between rucaparib exposure and PFS. Various rucaparib time-varying exposure measures were evaluated as shown in the following table.

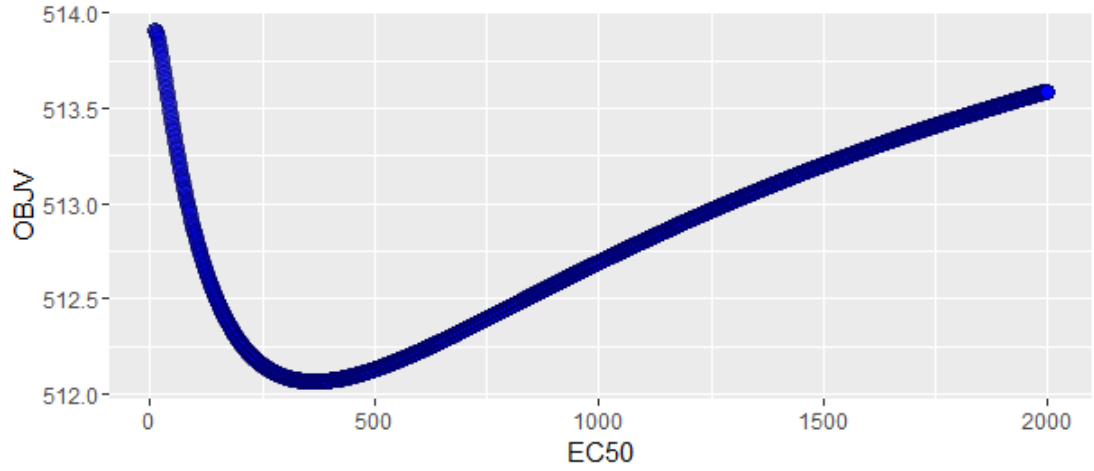
Exposure Metrics	Definition
Cavg1W	Average $C_{rucaparib}$ over prior one week at each day
Cavg2W	Average $C_{rucaparib}$ over prior two weeks at each day
Cavg3W	Average $C_{rucaparib}$ over prior three weeks at each day
Cavg4W	Average $C_{rucaparib}$ over prior four weeks at each day
CavgT	Average $C_{rucaparib}$ from the first dose at each day

The CAVG1W selected as the exposure metrics based on the model objective function value and biological plausibility. Nonlinear Emax model was adopted as described as the following equation.

$$h\left(t, X'_{ex}(t)\right) = h_o(t) \cdot exp\left(\beta_{ex2} \cdot X'_{ex}(t)\right); X'_{ex}(t) = \frac{X_{ex}(t)}{X_{ex}(t) + EC_{50}}$$

where $X_{ex}(t)$ is the rucaparib exposure measure which may vary with t, β_{ex1} represents the slope in the log-linear model, β_{ex2} represents the maximum drug effect in the Emax model, and EC50 represents a range of fixed values for the exposure at which half of the maximal effect is achieve. After screening over a grid of fixed EC50 values for CAVG1W ranging from 1 to 2000 ng/mL, the best value of EC50 was fixed as 365 ng/L (**Figure 14**).

Figure 14: Screening of EC50



.Source: FDA reviewer's analysis

A parameter summary for the best nonlinear model (EC50 = 365 ng/mL) is provided in the following table.

Table 8: Parameter Estimates for Exposure - PFS Model

Model	Parameter	Estimate	SE	P-value	OBJV
Emax	$\theta_{cavg1w\ (Emax)}$	-1.08	0.41	0.008	**512.07**
	$\theta_{PRTXGRP}$	2.05	0.76	0.007	
Linear	θ_{cavg1w}	-0.0002	0.0002	0.11	515.84
	$\theta_{PRTXGRP}$	*2.09*	0.76	0.006	
Log-linear	θ_{cavg1w}	-0.11	0.05	0.014	513.14
	$\theta_{PRTXGRP}$	2.18	0.76	0.004	

In addition, linear and log-linear model were also developed as sensitivity analysis. The model parameter estimates and E-R plot for these models are illustrated in Table 8 and Figure 15, respectively.

Figure 15: The relative risk (95% CI) of experiencing event (progressive disease or death) versus rucaparib exposure

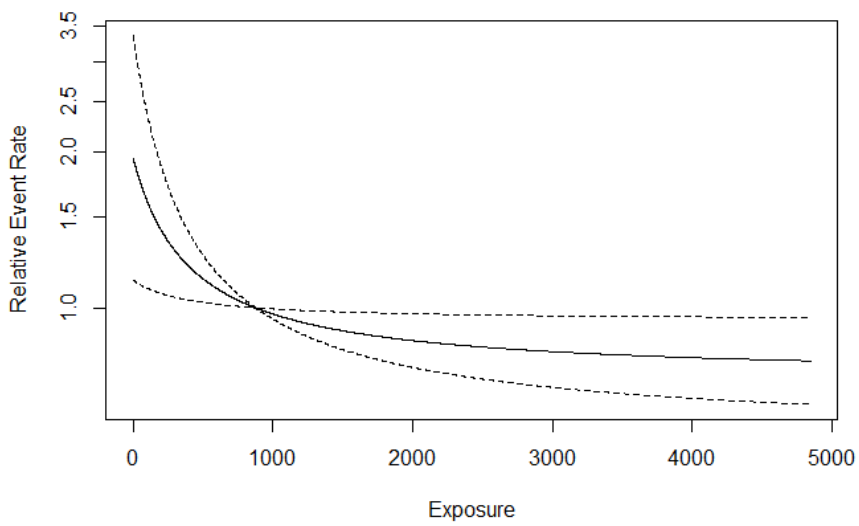
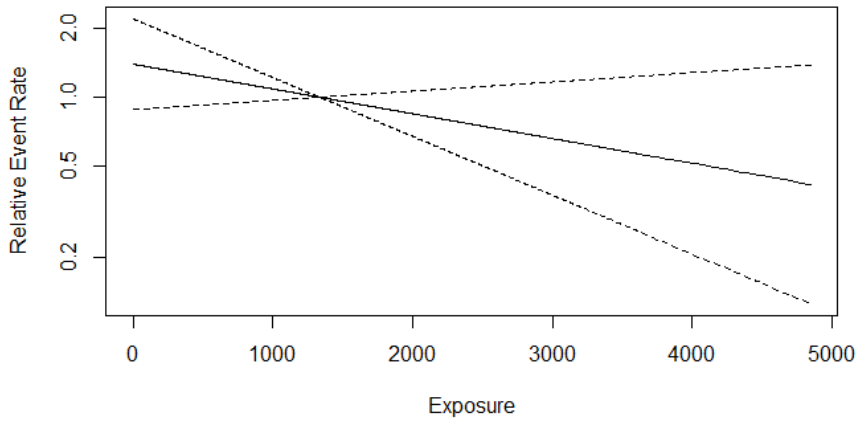
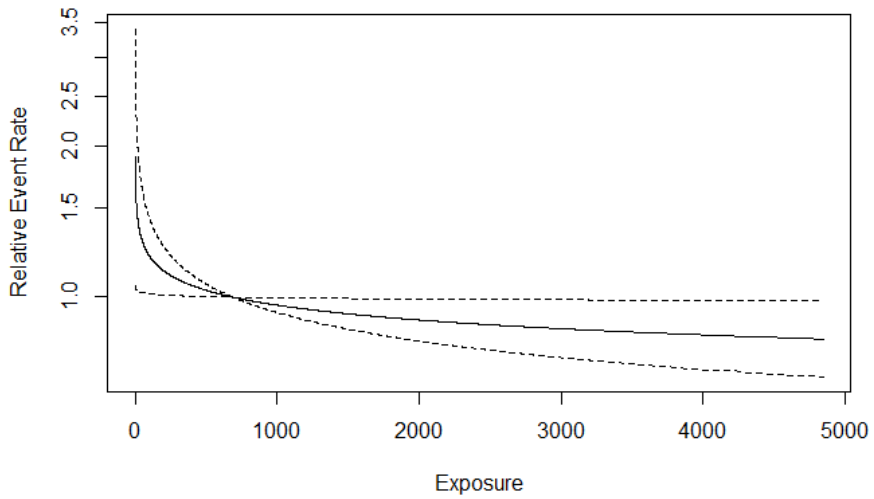
Emax	
Linear	
Log-Linear	
.Source: FDA reviewer's analysis	

Table 9 as shown below illustrate the impact of selected rucaparib exposure values on the predicted relative risk of progress free survival. The typical individual predicted average steady-state rucaparib

concentration for 200 mg (447 ng/mL), 400 mg (893 ng/mL), and 600 mg (1333 ng/mL) BID doses was used for exposure in the predictions. The exposure of 1333 ng/mL for 600mg BID is based on rucaparib concentrations that over the course of the study as predicted by the population PK model. Actual dosing history was used to generate the concentration-time profile and relevant PK metrics. The (447 ng/mL) for 200 mg and 750 ng/mL for 400 mg were predicted by scaling the exposure level at 600 mg BID in a dose-proportional manner, assuming the dose interruption/reduction profile is the same with lower dose levels. These numbers do not reflect the actual dosing irregularities which would be expected in observed data. This table illustrates the relative effect of different rucaparib concentrations on PFS in a relevantly ideal sense.

Table 9: Model Predicted Hazard Ratios for Progression Free Survival

Model Structure	**HR Relative to:**	**$AVCavg_{1W}$ = 1333 ng/mL (600 mg BID)**
Emax	447 ng/mL (200 mg BID)	0.78
	893 ng/mL (400 mg BID)	0.92
Linear	447 ng/mL (200 mg BID)	0.79
	893 ng/mL (400 mg BID)	0.89
Loglinar	447 ng/mL (200 mg BID)	0.89
	893 ng/mL (400 mg BID)	0.95

HR = hazard ratio

[a]Rucaparib concentrations correspond to the average concentrations for the 600 mg BID dosing regimen, and predicted average concentrations for 200 mg BID and 400 mg BID. Source: FDA reviewer' analysis

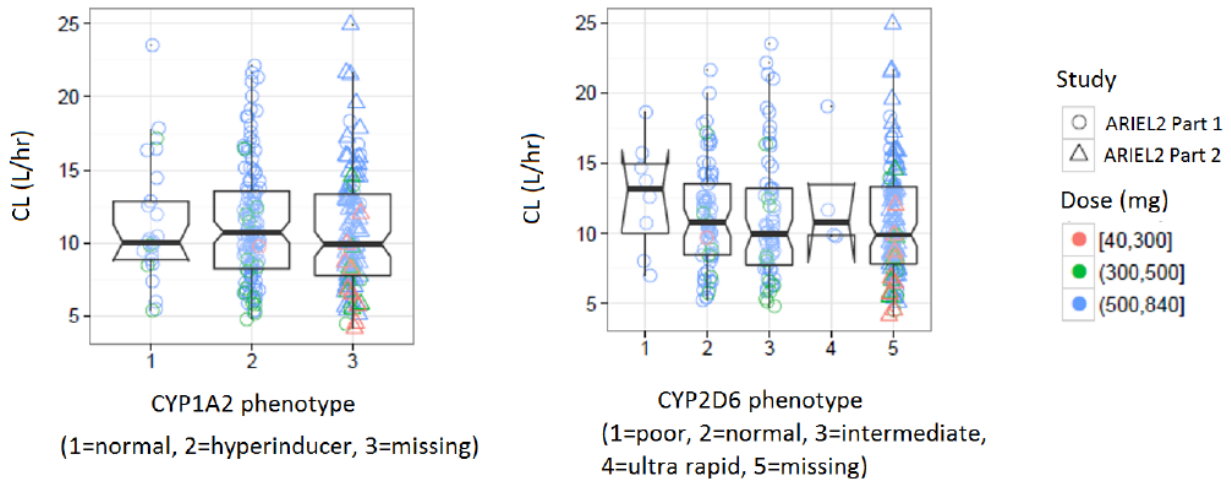
10.4.5. Genomic Factors

CYP1A2 and CYP2D6 genotype-predicted phenotypes and rucaparib PK

DNA isolated from blood samples collected at screening from 177 patients in parts 1 and 2 of Study CO-338-017 was genotyped for alleles in *CYP1A2* and *CYP2D6* that capture common genetic variation in these genes. Genotyping was performed using PCR-based multiplex reaction sets followed by MALDI-TOF mass spectrometry. Genotype-predicted phenotypes were assigned according to conventional pharmacogenetic designations except for CYP2D6 intermediate metabolizers. Patients with one functional and one nonfunctional *CYP2D6* allele are usually categorized as *CYP2D6* normal metabolizers

(PMID 24458010); however, the applicant categorized these individuals as intermediate metabolizers. In addition, sparse PK data were collected for all patients (N=300) on Cycle 1 Day 15, and on day 1 of subsequent treatment cycles. The impact of genetic variation in *CYP3A4* was not evaluated by the applicant. In general, *CYP3A4* genetic variation contributes only to a minor extent or only in specific populations (where loss-of-function variants are more common) to the inter-individual differences in the CYP3A4-mediated drug metabolism.

Genotype-predicted phenotypes and sparse PK data were available for CYP1A2 in 164 of 300 (55%) patients and for CYP2D6 in 160 of 300 (53%) patients. The phenotype data were included as covariates in the popPK model. Post-hoc estimates of rucaparib CL were compared among patients with different CYP1A2 and CYP2D6 phenotypes (Figure 1). For CYP1A2, the CL values were similar between normal metabolizers (n = 28) and hyper-inducers (n = 136). For CYP2D6, the CL values were largely overlapping among poor metabolizers (n = 9), intermediate metabolizers (n = 71), normal metabolizers (n = 76), and ultra-rapid metabolizers (n = 4). These data suggest that the tested CYP1A2 and CYP2D6 phenotypes do not significantly impact rucaparib PK, and drug-drug interaction potential of rucaparib as a CYP1A2 or CYP2D6 substrate is low. Although inconsistent with conventional pharmacogenetic designations, the discrepancy in the CYP2D6 phenotype categorization (intermediate instead of normal metabolizer) is unlikely to impact the applicant's results.



Source: Figure 8 in Report QS-CLV-006, Section 5.3.3.5.

Figure 1. Effects of CYP1A2 and CYP2D6 Phenotypes on Post-hoc CL

BRCA mutations and rucaparib efficacy

BRCA mutation testing:

The primary efficacy analysis population included 106 patients with BRCA-mutated ovarian cancer enrolled in two separate studies. Study CO-338-010 Part 2A enrolled 42 patients who harbored a deleterious germline BRCA mutation identified by a local laboratory test. Study CO-338-017 enrolled 64 patients (24 in Part 1 and 40 in Part 2) who harbored a deleterious BRCA mutation identified by either the clinical trial assay (CTA) or a local laboratory test. All patients received ≥ 2 prior chemotherapy regimens and received at least 1 dose of 600 mg rucaparib.

BRCA mutations were classified as germline, somatic or indeterminate based on the results of the CTA (an NGS-based assay that sequences DNA extracted from FFPE tumor specimens) and blood sample analysis using the BROCA-HR NGS-based assay and/or local laboratory testing. Patients with BRCA mutation- positive tumors using the CTA, but without germline BRCA results available, were classified as indeterminate.

The proposed CDx is a NGS-based test designed to detect *BRCA1* and *BRCA2* mutations by sequencing DNA extracted from FFPE tumor specimens but it cannot determine whether the mutation is germline or somatic. According to the applicant, a mutation is classified as deleterious if the sequence analysis identifies a premature stop codon anywhere in the *BRCA1/2* coding regions (except mutations located 3'of *BRCA2* K3326), variant splice sequences at intron/exon junctions -/+ 2 base pairs of exon starts/ends, or specific missense mutations from a curated list based on the Breast Cancer Information Core (BIC) database. (b) (4) ; however, these alterations were classified as BRCA-positive by the CTA. In addition, patients with large chromosomal rearrangements within intronic regions of *BRCA1/2* may have been classified as BRCA-positive based on local BRCA testing results; (b) (4) At the time of the NDA submission, tumor tissue was available for testing with the CDx in 53 patients included in the primary efficacy population; the presence of a deleterious BRCA mutation was confirmed with the CDx in 49 (92%) of these patients.

ORR in the primary efficacy analysis population and in selected subgroups:

Of 106 advanced ovarian cancer patients included in the primary efficacy analysis, 88 (83.0%) were determined to have a germline BRCA mutation, 13 (12.3%) were determined to have a somatic BRCA mutation (i.e., had a deleterious BRCA mutation detected in tumor tissue and not in whole blood specimen), and 5 patients had an indeterminate BRCA mutation type. *BRCA1* and *BRCA2* mutations were identified in 67 (63%) and in 39 (37%) patients, respectively.

The confirmed ORR was 53.8% [95% CI, 43.8%-63.5%,] by investigator assessment and 41.5% [95% CI, 32.0%-51.5%] by central IRR. Confirmed ORR (by investigator) was similar regardless of BRCA mutation type (germline vs. somatic) and BRCA gene mutation (*BRCA1* vs *BRCA2*; Table 1). Of note, of the seven patients who were refractory to platinum therapy, no objective responses were observed.

Table 1. Confirmed Objective Response Rate in Selected Subgroups

Subgroup	Investigator-assessed (N=106)
BRCA Gene	
BRCA1	53.7% (36/67)
BRCA2	53.8% (21/39)
Mutation Type	
Germline	53.4% (47/88)
Somatic	46.2% (6/13)
Platinum Sensitivity	
Sensitive	65.8% (52/79)
Resistant	25.0% (5/20)
Refractory	0.0% (0/7)

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/s/

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11 Statistical and Clinical and Evaluation

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11.1. Sources of Clinical Data and Review Strategy

11.1.1. Table of Clinical Studies

Table 1 lists the clinical trials used in the NDA submission and the sources of the safety and efficacy populations in the application. The primary evidence to support the clinical efficacy of rucaparib in patients with advanced ovarian cancer is from patients with ovarian cancer with BRCA mutations identified in the blood (genomic) or the tumor (genomic or somatic), who are platinum sensitive (>6 months progression-free following most recent platinum-containing regimen), and who had received treatment with at least two prior lines of platinum-containing chemotherapy. The efficacy population of 106 patients presented in the application is derived by pooling patients that meet these characteristics from two separate clinical trials, listed in the table: Study 10 and ARIEL2.

The primary data used to characterize the safety profile of rucaparib in patients with advanced ovarian cancer comes from a safety population of 377 patients with ovarian cancer treated on the same two trials and an additional supportive trial of 32 patients, known as RUCAPANC, CO-338-023.

Table 1 Listing of Clinical Trials Relevant to NDA 209115 Efficacy and Safety Populations

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled in efficacy and safety populations	Study Population	No. of Centers and Countries
CO-338-010 Study 10	Phase 1/2 Open label Single arm	Phase 1: Dose escalation Phase 2: (Parts 2A, 2B, 3): rucaparib 600 mg PO BID; 21-day cycles	Primary: Safety, MTD, PK, ORR by RECISTv1.1 Key Secondary: OS	Part 2A: 42	Part 1: Solid tumors Part 2A: gBRCAm patients with ovarian cancer after 2-4 prior treatment regimens Part 2B: tBRCAm patients with ovarian cancer after 3-4 prior treatment regimens Part 3: BRCAm solid tumors	11 sites: 4 US, 1 Canada 3 UK 2 Israel 1 Spain
CO-338-017 ARIEL2	Phase 2 Open label Single Arm	Rucaparib 600 mg PO BID; 21-day cycles	Primary: PFS (INV), ORR (INV) by RECISTv1.1 Key secondary: OS	Part 1: 24 Part 2: 40	Part 1: BRCAm platinum-sensitive ovarian cancer after ≥1 regimen Part 2: BRCAm platinum-sensitive ovarian cancer after 3-4 prior regimens	24 sites: 8 US 3 Australia 6 Canada 4 France 2 Spain 1 UK
Efficacy Population				**Total: 106**		
CO-338-010 Study 10	Phase 1/2 Open label Single arm	Phase 1: Dose escalation Phase 2: (Parts 2A, 2B, 3): rucaparib 600 mg PO BID; 21-day cycles	Primary: Safety, MTD, PK, ORR by RECISTv1.1 Key Secondary: OS	Part 1: 7 Part 2A: 42 Part 3: 26	Part 1: Solid tumors Part 2A: gBRCAm patients with ovarian cancer after 2-4 prior treatment regimens Part 2B: tBRCAm patients with ovarian cancer after 3-4 prior treatment regimens Part 3: BRCAm solid tumors	13 sites: 6 US 3 UK 2 Israel 1 Spain 1 Canada

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled in efficacy and safety populations	Study Population	No. of Centers and Countries
CO-338-017 ARIEL2	Phase 2 Open label Single Arm	Rucaparib 600 mg PO BID; 21-day cycles	Primary: PFS (INV), ORR (INV) by RECISTv1.1 Key secondary: OS	Part 1: 204 Part 2: 111	Part 1: BRCAm platinum-sensitive ovarian cancer after ≥1 regimen Part 2: BRCAm platinum-sensitive ovarian cancer after 3-4 prior regimens	50 Sites: 23 US 5 Australia 7 Canada 6 France 2 Spain 7 UK
CO-338-023 (RUCAPANC)	Phase 2 Open label Single Arm	Rucaparib 600 mg PO BID; 28-day cycles	Primary: ORR (INV) by RECISTv1.1	19	Adults with previously treated locally advanced or metastatic pancreatic cancer and a known deleterious BRCA mutation	5 Sites: 4 US 1 Israel
Safety Population				**Total: 409**		

11.2.3. **Review Strategy**

The FDA statistical and clinical NDA review consisted of one primary statistical reviewer and two primary clinical reviewers: one primary clinical reviewer of safety and one primary clinical reviewer of efficacy.

The NDA submission contained three single-arm trials: Study 10, CO-338-010, entitled, "A Phase 1/2, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Ovarian Cancer or Other Solid Tumor"; ARIEL2, CO-338-017, entitled, "A Phase 2, Open-label Study of Rucaparib in Patients with Platinum-sensitive, Relapsed, High-grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer,"; and RUCAPANC, CO-338-023, entitled, "A Phase 2, Open-Label Study of Rucaparib in Patients with Pancreatic Cancer and a Known Deleterious BRCA Mutation." Data from these three trials supported the efficacy and safety for the proposed indication.

The statistical and clinical review of efficacy focuses on an efficacy population of 106 patients drawn from the two ovarian cancer trials who meet the indicated clinical characteristics. The efficacy review includes a detailed review and analysis of data including the clinical study reports (CSR), case report forms (CRFs), statistical analysis plan (SAP), datasets, and programs.

The clinical review of safety focuses on a safety population of 409 patients treated with rucaparib from three trials that included ovarian cancer patients as well as patients with other tumors. The majority of the safety analyses were performed on the ovarian cancer patient population (378 patients). The safety review includes a detailed review and analysis of data including the CSR, CRFs, narrative and datasets. The clinical review of safety was supplemented with an evaluation of the AE of special interest, MDS/AML, in patients treated with rucaparib on trial.

The statistical and clinical review of safety and efficacy included the following:

- Review of current literature on ovarian cancer epidemiology and treatment
- Review of clinical trials Study 10, ARIEL2, and RUCAPANC, including CSR, protocol, protocol amendments, SAP, and SAP amendments
- Review and assessment of Applicant analyses of rucaparib safety and efficacy in the CSR
- Review and audit of datasets and SAS programs
- Review of patient narratives of clinical endpoints
- Review of patient narratives of serious adverse events and deaths
- Review of minutes of meetings conducted during rucaparib development
- Review of Module 2 summaries, including the Summary of Clinical Efficacy, Summary of Clinical Safety, and proposed labeling for rucaparib
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Data Sources

The electronic submission, including protocols, SAP, CSRs, datasets in SDTM and ADAM formats, and SAS codes for the NDA are located in the following network path:
(b) (4)

Data Analysis and Quality

The Applicant has averred that the trials included in this application were conducted in accordance with legal and regulatory requirements, the general principles as set forth in the US Code of Federal Regulations (21CFR 50, 56, and 312), as well as International Conference on Harmonization (ICH) for GCP 1996, and the Declaration of Helsinki (World Medical Association 2013). Charters for independent radiology review and pathology for custody of clinical samples were provided in the application.

The quality and integrity of the submitted data was audited from eCRF and no errors were discovered. Analyses performed by the Applicant were reproducible by the statistical and clinical reviewers based on the submitted data, including reproduction of the efficacy and safety patient populations. ADaM datasets reflected source data from SDTM datasets. CDER's OCS JumpStart service performed an initial data assessment and high-level safety review. Data integrity and formatting from this review was found to be good.

Requests for information for clarification of questions that arose during the review were submitted electronically to the Applicant. Review of the applicant's responses to these information requests (IRs) were important to:

- Reproduce the Applicant's selection of pooled efficacy and safety populations
- Reproduce the Applicant's efficacy results from SDTM datasets
- Conduct FDA analyses of duration of response (DOR)
- Evaluate the exposure-response relationships in greater detail
- Evaluate the activity of the clinical trial assay (CTA) and companion diagnostic device (CDx) in development by Foundation Medicine Inc.
- Evaluate clinical sites and determine clinical sites for OSI inspection

11.3. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy analyses are based on data generated from select patients treated on two clinical trials: ARIEL2 and Study 10. Sections 11.2.1 and 11.2.3 provide details of these study designs.

11.1.1. Study CO-338-017, "ARIEL2"

Trial Design and Endpoints

ARIEL2 is a two-part, phase 2, open-label, single-arm, multi-center trial to evaluate the efficacy of rucaparib 600 mg PO BID in women with relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer after they had been treated with prior platinum-containing chemotherapy. The trial is ongoing, and therefore interim data are provided for this marketing application; the data analysis to support evaluations of safety and efficacy are presented in the integrated summaries of safety and efficacy, and are not themselves part of the statistical analysis plan of this trial as described in the protocol document.

The trial enrolled patients into three prospectively-defined subgroups (described below) using a homologous recombination deficiency (HRD) genetic signature designed by companion diagnostic device manufacturer Foundation Medicine Inc. This score is derived from DNA extracted from FFPE tumor specimens, and is putatively a measure of genomic "scarring" as a result of mutations in genes in DNA repair pathways that could hypothetically render tumors susceptible to PARP inhibition, including BRCA1 and BRCA2. The primary purpose of the study is to characterize the relationship between HRD status and rucaparib efficacy and enable identification of patients without BRCA mutation who are likely to derive benefit from treatment with rucaparib. The primary objective in parts 1 and 2 was to determine investigator-assessed PFS by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the three HRD subgroups, defined below.

All patients were required to provide tumor tissue for analysis, which could either be a screening biopsy and/or archival FFPE tumor tissue; based on the results of the HRD test, patients were prospectively classified into one of three groups as defined by the clinical trial assay (CTA). Results that revealed a deleterious BRCA 1/2 mutation in tumor tissue resulted in classification into the tBRCA mutation subgroup. Patients without BRCA mutation were classified into either non-BRCA/LOH + and non-BRCA/LOH – as a function of genome-wide loss of heterozygosity (LOH). Based on discussion with FDA, the application for accelerated approval of rucaparib focused on the group with tBRCA mutation.

Notably, the non-BRCA/LOH+ subgroup were discussed at meetings with the Applicant (August 20, 2015), and response rates for patients with a pre-specified LOH cutoff of 14% was 17 % (6/35) in patients with a history of treatment with >1 prior chemotherapy regimens; during these discussions, the Applicant was advised to focus on the tBRCAm patient population, as response rates in this group, including patients who had had treatment with at least two prior chemotherapy regimens, was more robust.

All patients were treated with the RP2D of rucaparib, 600 mg PO BID continuously in 28-day cycles until unacceptable toxicity, patient/investigator request to discontinue, disease progression, or death. Dose reductions and withholding are described in detail below. Doses were administered without regard to food.

Efficacy measures for this trial included tumor assessments (clinical examination and imaging using primarily computed tomography of the chest, abdomen, and pelvis per RECIST), while other studies (MRI, X-ray, PET, U/S) were performed if necessary. Tumor assessments were performed at screening

and at the end of every 8 weeks of treatment, and at treatment discontinuation unless radiologically demonstrated disease progression was the reason for discontinuation. Confirmatory scans were required after at least 4 weeks following initial radiographic response. Copies of CT scans were collected retrospectively for patients in study part 1 and prospectively for patients in study part 2. CA-125 measurement, though not a regulatory endpoint, was measured every cycle.

Part 1 of the trial enrolled patients who had been treated with at least one prior platinum-based regimen and had platinum-sensitive disease. Patients were required to have disease that was measurable by RECIST v1.1 and amenable to biopsy. Enrolment of patients known to harbor deleterious gBRCA mutation was limited to 15 to ensure sufficient power for the comparison of the non-BRCA HRD subgroups. Patients who had been treated with one prior chemotherapy regimen were excluded from the efficacy population for the ISE.

Enrolment in part 1 began in October 2013, and completed in December 2014, at 50 sites in six countries, including 23 sites in the US, with 204 patients treated during this part of the study. Of these, 40 patients were identified with deleterious BRCA mutation in tissue (tBRCAm) based on CTA results. BRCA mutation by CDx was performed on a subset of these patients.

Study part 2 followed a protocol amendment to evaluate rucaparib efficacy in ovarian cancer patients who had undergone treatment with 3 or 4 prior chemotherapy regimens, with the goal of further evaluating efficacy in a more heavily pretreated group irrespective of platinum sensitivity; thus, platinum-resistant and platinum-refractory patients were enrolled along with patients who were platinum sensitive. Resistant/refractory patients were permitted who may have had prior non-platinum treatment regimens

Enrolment into part 2 began in March 2015, with 111 patients treated with rucaparib by enrolment cutoff date of October 1, 2015, for the efficacy evaluation for this application. Patients were classified into one of three subgroups as described above, with 38 patients identified as having tBRCAm by CTA, of which a subset were later confirmed by CDx.

FDA's review of efficacy is limited to analysis of ORR and duration of response for the efficacy population (*BRCA*m advanced ovarian cancer treated with at least two chemotherapies) in this single-arm application. The data cutoff dates for these analyses include: patient enrollment cutoff of October 1, 2015, and a study visit data cutoff of February 29, 2016. There were 315 patients enrolled and with data available as of the cutoff date. As a result of these data cutoff dates for the ongoing trial, several analyses planned in the trial were not performed for this application, and will be conducted upon completion of the trial.

Inclusion Criteria:

Patients who fulfilled all of the following criteria were eligible for enrollment. Unless otherwise specified, the criteria below apply to patients enrolled in either Part 1 or Part 2 of the trial.

1. Have signed an IRB/IEC-approved ICF prior to any study-specific evaluation.

2. Have been ≥ 18 years of age at the time the ICF was signed.

3. Had a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- If mixed histology, > 50% of the primary tumor must have been confirmed to be high-grade serous or endometrioid upon re-review by local pathology.
- Patients with a histology other than serous or endometrioid were also eligible for Part 2 of the trial if they were known to harbor a deleterious / pathogenic BRCA mutation (germline or somatic).

4. Had relapsed/progressive disease as confirmed by radiologic assessment.

5. Part 1: Received prior platinum-based therapy and have platinum-sensitive disease:

a. Received ≥ 1 prior platinum-based treatment regimen; AND

b. Received a platinum-based regimen as their last treatment; continuous or switch maintenance treatment as part of this regimen is permitted (hormonal treatment was permitted following the last platinum regimen with advance approval from the sponsor); AND

c. Was sensitive to the last platinum regimen. Platinum-sensitive disease is defined as documented radiologic progression ≥ 6 months after the last dose of platinum administered in the treatment setting.

Part 2: Received at least 3, but no more than 4, prior chemotherapy regimens and had documented treatment-free interval of ≥ 6 months following first chemotherapy regimen received.

a. Hormonal agents (eg, tamoxifen, letrozole, etc), anti-angiogenic agents (eg. bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc), and other non-chemotherapy agents administered as single agent treatment were not counted as a chemotherapy regimen for the purpose of determining patient eligibility.

b. Agents administered in the maintenance setting were not counted as a separate regimen.

6. Part 1 only: If < 55 years of age at diagnosis, or had prior history of breast cancer, or had close relative (first or second degree) with ovarian cancer or early onset (< age 50) breast cancer, must have been previously tested for gBRCA mutation; after 15 patients harboring the gBRCA mutation were enrolled, no additional patients with a known gBRCA mutation were to be allowed to enroll.

7. Had undergone a biopsy of tumor tissue prior to first dose of study drug and had the tumor tissue confirmed by the central laboratory as being of adequate quality (at least

20% tumor content with a minimum of 80% nucleated cellular content). Note: biopsy was optional for Part 2 patients known to harbor a deleterious gBRCA mutation.

- If tumor tissue obtained from the biopsy was deemed inadequate, and the patient was unwilling or unable to have another biopsy, the patient could be considered for enrollment if archival tumor tissue was provided and deemed of adequate quality. This must have occurred prior to any treatment with rucaparib.

  a. Biopsy must have been of solid tumor tissue; ascites was not acceptable.

  b. Biopsy must have been of sufficient yield for planned analyses.

8. Had sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue available for planned analyses; cytospin blocks from ascites were not acceptable.

   - The most recently obtained tumor tissue that was of adequate quality (at least 20% tumor content with a minimum of 80% nucleated cellular content) was to be submitted.

9. Had measurable disease as defined by RECIST Version 1.1 in addition to the lesion planned for biopsy; a single RECIST target lesion would suffice if, in the investigator's opinion, it was of sufficient size that the biopsy would not affect postdose RECIST evaluations.

10. Had adequate organ function confirmed by the following laboratory values obtained within 14 days prior to the first dose of rucaparib:

    a. Bone marrow function

       i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

       ii. Platelets $> 100 \times 10^9$/L

       iii. Hemoglobin ≥ 9 g/dL

    b. Hepatic function

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

       ii. Bilirubin ≤ 1.5 × ULN (< 2 × ULN if hyperbilirubemia was due to Gilbert's syndrome)

       iii. Serum albumin ≥ 30 g/L (3 g/dL) (Part 2 only)

    c. Renal function

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

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

Exclusion Criteria:

Patients who met any of the following criteria were excluded from the study:

1. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which she may have been (but not necessarily) currently receiving treatment.

    a. Patients with a history of malignancy that had been completely treated, with no evidence of that cancer currently, were permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant (BMT) > 2 years prior to first dose of rucaparib

2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib were eligible.

3. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases were eligible provided they had been clinically stable for at least 4 weeks.

4. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib.

5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome.

    (AIDS)-related illness, or history of chronic hepatitis B or C.

6. Pregnant or breast feeding. Women of childbearing potential must have had a negative serum pregnancy test < 3 days prior to first dose of rucaparib.

7. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment was less than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen could be permitted with prior advanced approval from sponsor).

8. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤ 7 days prior to first dose of rucaparib or had on-going requirements for these medications.

9. Non-study related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must have been sufficiently recovered and stable before treatment administration.

10. Presence of any other condition that may have increased the risk associated with trial participation or may have interfered with the interpretation of trial results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the trial.

11. Diagnosis of low-grade serous or Grade 1 endometrioid ovarian cancer.

12. Part 2 Only: Hospitalization for bowel obstruction within 3 months prior to enrollment.

Dose Modification and Management Algorithms

During the trial, treatment with rucaparib was held and dose reduction considered for grade 3 or 4 hematologic toxicity, grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled; at investigator discretion, rucaparib was continued if ALT/AST elevation reached grade 3 but bilirubin was < institutional ULN and ALP was < 3x ULN, but held if ALT/AST did not decline to grade 2 within two weeks). Investigators also had discretion over rucaparib dose reduction/withholding in the event that grade 2 toxicity was not adequately controlled. Treatment withholding was to continue until toxicity resolved to ≤ grade 2, with resumption at either the same or lower dose level. If resumed at the same dose level, if toxicity recurred/continued, dose reduction was warranted. Table 2 describes dose reductions prespecified in the trial. Patients in part 1 initially were treated with 60 mg or 120 mg tablets; in part 2, patients were treated with 300 mg or 200 mg tablets.

Treatment with rucaparib was to be held if any of the following were observed and a dose reduction was to be considered:

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines)

  Note: Rucaparib administration was permitted in the event of Grade 3 elevations of ALT/AST provided bilirubin was < ULN and alkaline phosphatase was < 3x ULN and there were no other signs of liver dysfunction. Rucaparib was to be held if ALT/AST did not decline within 2 weeks or continued to rise, and rucaparib treatment could resume at either the current dose or reduced dose upon resolution to ≤ Grade 2 ALT/AST (added in Protocol Amendment 4).

- In addition, and at the discretion of the investigator, the dose of rucaparib could be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Treatment with rucaparib was to be held until the toxicity resolved to ≤ CTCAE Grade 2. Twice daily (BID) dosing could then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment was resumed at the same dose, and the patient experienced the same toxicity, the dose was to be reduced following resolution of the event to ≤ CTCAE Grade 2. If the patient continued to experience toxicity, additional dose reduction steps were permitted. If a patient continued to experience toxicity despite multiple dose reduction steps, or if dosing with rucaparib was interrupted for >14 consecutive days due to toxicity, treatment was to be discontinued, unless otherwise agreed between the investigator and the sponsor.

Dose reduction steps are presented in Table 2.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 was permitted upon agreement between the investigator and sponsor.

Table 2 Rucaparib dose reduction steps for ARIEL2

Tablets	60/120 mg	300/200 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
*Consultation with medical monitor required before reducing to dose level -3		

Source: ARIEL2 protocol amendment 4, Table 3, page 52

Monitoring Plan

Table 3 below includes the monitoring plan for ARIEL2 part 1.

Procedure[a]	Screening Phase	Treatment Phase (± 3 days of scheduled timepoint)			Post-Treatment Phase		
		Cycle 1		Cycles 2+			
	Day -28 to Day -1	Day 1[b]	Day 15	Day 1	End of Treatment	28 Day Follow-up (FU) (28 ± 3 days after	Long-term FU
Informed Consent[c]	X						
Medical/Oncology History[d]	X						
Physical Examination[e], Height[e], Weight	X	X		X	X		
ECOG Performance Status	X	X		X	X		
Vital Signs	X	X[f]		X[f]	X		
Adverse Events[g]	X	X	X	X	X	X	
Prior/Concomitant Medications and Procedures	X	X	X	X	X		
12-lead ECG[h]	X				X		
Hematology[i] (local lab)	X[j]	X	X	X	X		
Serum Chemistry[k] (local lab)	X[j]	X	X	X	X		
Pregnancy Test[l] (WOCBP only) (local lab)	X			X	X		
Urinalysis[m] (local lab)	X						
Disease Assessment/Tumor Scans[n]	X			X[o]	(X) [p]		X[q]
CA-125 Measurement	X[r]	X		X[s]	X		
Tumor Tissue Biopsy	X[t]				(X)[u]		
Archival Tumor Tissue	X[v]						
Blood Sample for ctDNA Analysis[w] (central lab)	X	X		X	X		
Blood Sample for Storage (central lab)	X						
Rucaparib Dispensation/Administration/ Accountability		X		X	X		
Plasma PK Sample[x] (central lab)			X	X[y]			
Serum AAG Sample[w] (central lab)			X	X[y]			
Part 2 Only: Survival, Subsequent Treatments, and Secondary Malignancy							X[z]

Abbreviations: AAG = alpha-1 acid glycoprotein; ALP = alkaline phosphatase; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BUN = blood urea nitrogen; CR = complete response; CT = computer tomography; ECG = electrocardiogram; HDL= high- density lipoprotein; IRR = independent radiology review; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC, = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; SAE = serious adverse event; WBC = white blood cell; WOCBP = women of childbearing potential.

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

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

[c] = Consent could be completed outside the 28 screening window as consent does not expire. Reconsent was not required if outside the screening window.

[d] = Patient's medical record must have included prior treatments received, dates of administration, date of progression, and radiology report(s) and/or CA-125 results to support assessment of disease progression. gBRCA test results, if known, were also to be captured.

[e] = A complete physical examination was to be performed at screening and the End of Treatment Visit; a limited physical examination could be performed at all other visits. Height at screening only.

[f] = Vital signs (blood pressure, pulse, and temperature) was to be taken on clinic visit days.

[g] = AEs were recorded from the time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs were followed to resolution.

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

[i] = Included hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count (all patients in Parts 1 and 2; patients in Part 2 were also required to have MCV, MCH, and MCHC and reticulocyte count measured). Blood was to be analyzed by a local laboratory and results had to be reviewed by the investigator prior to dosing with rucaparib.

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

[k] = Included total protein, albumin, creatinine or estimated GFR using Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus (all patients in Parts 1 and 2; patients in Part 2 were also required to have a lipid panel that included LDL, HDL and triglycerides in addition to the total cholesterol measurement; the lipid panel did not require fasting). Blood was to be analyzed by a local laboratory and results had to be reviewed by the investigator prior to dosing with rucaparib. In the event that ≥ Grade 2 AST elevations were observed, the investigator was to consider performing the following additional tests: GGT, CK/CPK, and PT.

[l] = Women of childbearing potential must have had a negative serum pregnancy test result < 3 days prior to the first dose of rucaparib. A serum or urine pregnancy test (investigator's discretion) had be performed < 3 days prior to Day 1 of every cycle during the treatment phase. A serum pregnancy test had to be performed at the End of Treatment Visit.

[m] = Included dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings were abnormal, performed microscopic evaluation.

[n] = Disease assessment included clinical examination, CA-125 (if applicable), and appropriate imaging techniques, including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) could be performed if required. The same methods used to detect lesions at baseline were to be used to follow the same lesions throughout the clinical study. If a patient had known brain metastases, this disease was to be evaluated at each required assessment. Copies of CT scans were to be collected from all patients in Part 2 of the study and could be collected from selected patients in Part 1 of the study. Independent radiology could be conducted on all or a subset of CT scans.

[o] = Tumor scans were to be performed at the end of every 8 weeks (± 4 days) while on study. A confirmatory scan was to be performed ≥ 4 weeks after an initial response of PR or CR was observed. Patients who had been on study at least 18 months, could decrease the frequency of disease assessments to every 16 (± 2) weeks.

[p] = Disease assessments were also to be done at the time of treatment discontinuation if it had been ≥ 8 weeks since the last assessment.

[q] = To be performed at the end of every 8 weeks (± 4 days) until radiologically confirmed disease progression, death or initiation of subsequent treatment for any patient who discontinued from study treatment for reason other than disease progression or death. Patients who had been on study at least 18 months could decrease the frequency of tumor scans to every 16 (± 2) weeks.

[r] = To be evaluable for CA-125 response, at least 2 pretreatment samples must have been collected at least 1 day, but not more than 3 months, apart. At least 1 sample was to be within 1 week prior to the first dose of rucaparib. Both samples had to be ≥ 2X the ULN for CA-125 response assessment.

[s] = CA-125 measurement were to be done on Day 1 of every cycle, at the end of treatment, and as clinically indicated.

[t] = Screening biopsy must have been collected within 28 days and at least 7 days prior to first dose of study drug. Biopsy sample must have been of solid tumor tissue; ascites was not acceptable. This screening sample had to be sufficient for the planned analyses and deemed of adequate quality by the central laboratory prior to enrollment of patient into the study. The Pathology Charter provided detailed sample handling instructions. If a biopsy was recently performed as standard of care prior to this patient consenting to this study or after study informed consent but outside the 28 day screening window this could be acceptable with advance approval from the sponsor. Note: the screening biopsy sample was optional for Part 2 patients known to harbor a deleterious gBRCA mutation.

[u] = An optional post-treatment tumor biopsy sample could be collected from patients who progressed on rucaparib. If the progression was due to new lesions, the preference was to obtain the biopsy from the new lesion(s). Additional consent was required. The Pathology Charter provided detailed sample handling instructions.

[v] = The presence of adequate archival tissue for planned analyses had to be confirmed during screening; however, shipment of archival tumor tissue was not required prior to enrollment. The Pathology Charter provided detailed sample handling instructions.

[w] = Collected and processed for plasma. The Laboratory Manual provided detailed sample processing instructions.

[x] = A single sample was to be collected as close to 12 hours after the last dose was taken as possible and prior to the next dose. The Laboratory Manual provided sample processing instructions.

[y] = Cycles 2, 3, and 4 only.

[z] = All Part 2 patients discontinued from treatment, regardless of reason, were to be followed for survival, subsequent therapies, and secondary malignancy every 12 weeks until death, loss to follow-up, withdrawal of consent from study or study closure, whichever happened first. Follow-up could be performed via the telephone. Diagnosis of any secondary malignancy required appropriate documentation (i.e., laboratory and/or pathology reports).

Source: Table 4, page 58, ARIEL2 protocol v 4 dated December 19, 2014

Adverse Event Collection

Patients were monitored for AEs during study participation (beginning at the time informed consent is obtained) and until 28 days after the last dose of rucaparib. The existence of an AE could be concluded from a spontaneous report of the patient, from the physical examination, or from specific tests such as the ECG, laboratory assessments, or other study-specified procedure. Each AE was evaluated by the investigator for duration, severity, seriousness, and causal relationship (not related, related) to the study medication. The action taken and the outcome were also recorded. AEs and laboratory abnormalities were graded according to the NCI CTCAE grading system (Version 4.03) and recorded on the eCRF. For any term that was not specifically listed in the CTCAE, intensity was to be assigned a grade of 1-5 using the CTCAE guidelines as listed in the protocol.

Statistical Analysis Plan

The primary efficacy endpoint of part 1 is investigator-assessed PFS, while for part 2, the primary efficacy endpoint is investigator-assessed objective response rate (ORR); independent radiology review (IRR) is a supportive analysis for all or a subset of patients. The ARIEL2 statistical analysis plan provides for efficacy evaluations presented by HRD status and study part (parts 1 and 2). Analysis of PFS is planned for the safety population, with ORR and CA-125 response rates presented for the efficacy evaluable population; the efficacy population for this study includes all patients evaluable for response by RECIST and/or CA-125 criteria.

Secondary efficacy analyses include ORR for part 1 for the efficacy evaluable population, supported by IRR, as well as duration of response, and overall survival.

Additionally, the predictive utility of the HRD diagnostic test is to be evaluated by comparing the primary and secondary endpoints in the tBRCAm subgroup to that of the non-BRCA, HRD+ (nbHRD), and biomarker negative subgroups.

This study design was a novel approach to establishing a next-generation sequencing (NGS)-based companion diagnostic device discussed in the Integrated Summary of Efficacy (ISE), but this study as written and the associated companion diagnostic are still in clinical development. The three molecular subgroups established in this trial for the purposes of evaluating the HRD score will not be analyzed as part of this application. Instead, all identified patients fitting the inclusion criteria (including germline and somatic BRCA mutation-carrying tumors) are aggregated in the ISE for this application. All patients treated with rucaparib 600 mg PO BID are included in the safety population, presented in the integrated summary of safety (ISS). The analysis plan specified in the ARIEL2 protocol is not applied in this application.

Sample size considerations

ARIEL2 was designed as a single arm study, for a planned enrollment of 480 patients, 180 in part1 and 300 in part 2, with the goal of recruiting 180 patients into each subgroup (tBRCAm, nbHRD, and

biomarker negative). The size of the subgroups was estimated based on frequencies of HRD-associated genetic abnormalities at initial diagnosis as reported in the literature, and the hypothesis that platinum sensitivity will enrich the population for patients with HRD tumors. The SAP details the planned analyses for the study. For part 1 of the study, with 180 patients enrolled, comparison of any two subgroups was predicted to contain about 100 patients, providing 80% power at a 2-sided 10% significance level to detect a difference in PFS distributions, with the assumption of the hazard ratio between the groups is 0.50. The objective of part 2 is to estimate ORR in each HRD subgroup in a more heavily-pretreated population. The goal of enrolling 300 patients into this part of the trial is in order to enroll at least 80 patients in each HRD subgroup.

Because the efficacy population for the application is drawn from two different single arm studies having different study objectives, and primarily because the nbHRD population is not included in this efficacy population, the individual statistical analysis plans and sample size considerations applied in the individual protocols are not the subject of this application. Further descriptions of the sample size of the safety and efficacy populations for this application are summarized in the integrated summary of efficacy and the integrated summary of safety, below.]

Protocol Amendments

The original protocol was dated 7 May 2013. As of the 29 February 2016 visit data cut-off for the non-prespecified interim CSR, the protocol had been amended 4 times. A summary of major changes at each amendment is presented in Table 4 below.

Table 4 Summary of Key Protocol Amendments in ARIEL2

	Date	Details of Amendment
Amendment 1	19 August 2013	• Starting dose was established as 600 mg rucaparib BID. This dose was selected based on safety, tolerability, overall PK, and the preliminary efficacy profile observed in the CO-338-010 study and because although no dose-limiting toxicities (DLTs) had been observed in the CO-338-010 study, myelosuppression had been observed beyond Cycle 1 at doses ≥ 480 mg rucaparib BID. • Language was added to allow a reduction in starting dose if warranted • Safety language regarding AE management and assessment was added for ALT and AST elevations • Language was clarified to reflect that ORR would consist of an integrated assessment of RECIST Version 1.1 and GCIG CA-125 response. • The option of collecting and testing ascites samples was removed.

	Date	Details of Amendment
Amendment 2.1	30 May 2014	• HRD subgroups were revised to include groups with tumor genomic LOH (high or low), as well as BRCA1/2 gene mutation. • The primary objective, and associated endpoint, was changed from (b) (4) to efficacy as defined by PFS. • Inclusion criteria were modified including: Criterion 5: Revised to indicate that hormonal treatment after the most recent platinum-based regimen could be permitted with approval from the sponsor Criterion 6: Clarified that once the gBRCA enrolment cap was reached, patients known to have a deleterious gBRCA mutation were not eligible Criterion 8: Revised to clarify that the most recently collected tumor tissue that was of adequate tumor content was to be submitted for analysis rather than the oldest available tissue. • Exclusion criteria were modified including: Criterion 11: Added diagnosis of low-grade serous or Grade 1 endometrioid ovarian cancer. • Rucaparib does not have to be held for Grade 3 elevations of ALT/AST if not accompanied by other signs of liver dysfunction • Added language to specify that patients enrolled into Part 1 and Part 2 would receive 120 and 300/200 mg tablets, respectively, when initiating treatment. Once available supplies of 120 mg tablets were exhausted patients who were ongoing in Part 1 could be transitioned to 300/200 mg tablets. • GCIG CA-125 response criteria were modified to only require 1 predose sample.
Amendment 2.1 (continued)	30 May 2014	• Changes to statistical analyses included: Clarified that data would be summarized separately for Part 1 and Part 2 and may also be pooled as appropriate. Included a rationale for the Part 2 sample size and the specifics of how ORR was to be assessed. • Specified that IRR could be performed as a supportive analysis for all (Part 1 and Part 2) or a subset of patients.

Source: ARIEL2 protocol

Reviewer Comment:

The amendments applied by the applicant to this trial were not felt to significantly alter trial potential for demonstrating efficacy, and without increasing safety concerns, or impacting the benefit-risk assessment of the trial results.

11.1.2. Study Results for Study CO-338-017, ARIEL2

Compliance with Good Clinical Practices

The applicant stated in the clinical study report for trial ARIEL2 submitted with the application that the study was conducted in accordance with procedures intended to ensure adherence to the requirements of Good Clinical Practice (GCP). The applicant went on to state that the study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the US Code of Federal Regulations (CFR, Title 21 CFR § 50, 56, and 312), International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Conference on Harmonization (ICH) Guidelines for GCP 1996, and the Declaration of Helsinki (World Medical Association 2013).

Financial Disclosure

The applicant submitted a list of investigators (NDA module 1.3.4) and forms 3454 that certify that most investigators participating in the study had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the studies. Financial disclosures and forms 3455 were provided for two investigators. (b) (6) is listed as having received > $25,000 for sponsorship of a research project entitled, (b) (6) that (b) (6)). (b) (6) is listed on the patent for rucaparib and its use in ovarian cancer, though the included memorandum states that she would not receive any remuneration associated with the patent, and that any such would remit to her employer, (b) (6)

Reviewer Comment:
It is unlikely that financial bias impacted the trial because (b) (6) *patient into ARIEL2, as did* (b) (6)

Patient Disposition

Patient disposition for the efficacy and safety populations respectively is presented in the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS). A summary of patient disposition for the included safety population of 315 patients is presented in Table 5.

Table 5 Summary of Patient Disposition for Safety Population on ARIEL2

	Safety Population N=315 n (%)
End of treatment status	
Ongoing	49 (16)

Discontinued	266 (84)
Primary discontinuation reason	
Progressive disease	218 (69)
Adverse event	26 (8)
Death	0
Withdrawal by patient	18 (6)
Physician decision	3 (1)
Other*	1 (.3)

Source: ADSL.xpt, reviewer JMP analysis
**Other included one patient who was discontinued in error—discussed below in protocol deviations.*

Reviewer Comment:

The applicant had coded three patient dispositions as "other;" however, upon evaluating the submitted data, one of these patients withdrew with adverse events, and another withdrew upon tumor diameter increase of <20% but at the patient's behest. These were recoded for this analysis.

Protocol Violations/Deviations

Protocol deviations including inclusion/exclusion criteria deviations and major protocol deviations did result in treatment discontinuation for one patient in the safety population for this study.

A total of 9 patients had eligibility deviations: 8 in part 1, and 1 in part 2. There was one patient with a prior history of tubal breast cancer who underwent curative treatment within 5 years; the Applicant provided a waiver for this patient and amended the protocol such that only active malignancy would be excluded. Another patient had a screening biopsy 63 days prior to dosing instead of the 28 days mandated in the protocol; the applicant provided a waiver, and amended the protocol to allow standard-of-care biopsies with a waiver. This patient also had a history of diverting ileostomy, which deviated from exclusion for upper bowel removal; this was later clarified in amendment 2.1. One patient took clarithromycin, a strong CYP3A4 inhibitor, within 7 days of starting rucaparib. One patient aged < 55 years did not have previous gBRCA testing. Two patients had hormonal therapies after platinum (one with letrozole, one with tamoxifen) with progression, two patients had disease progression less than 6 months from last platinum, and one patient had two prior chemotherapy regimens versus the 3-4 required, and a waiver was provided.

Patient 14001-508 in part 2 had incorrectly measured sum of largest diameters of target lesions miscalculated, resulting in an erroneous assessment of PD with a true assessment of SD, resulting in the patient being removed from treatment in error.

Another patient erroneously took rucaparib 900 mb BID for 9 days before the error was rectified and the patient resumed 600 mg BID.

Reviewer Comment:

These deviations were deemed to not significantly impact the integrity of the study and the production of data of sufficient quality to support the safety and efficacy analyses presented in the integrated summaries of efficacy and safety.

Table of Demographic Characteristics

As of October 1, 2015, the enrollment cutoff date for patients included in the CSR for this application, 50 sites enrolled patients in ARIEL2; 27 of these sites were outside of the United States. Of patients in the application safety population, 315 were drawn from this study, from the U.S. and 27 extra-U.S. sites; of the efficacy population, 64 were from this study, from the U.S. and 16 extra-U.S. sites. The demographics and baseline characteristics for this study are aggregated for the efficacy and safety analyses and presented in the ISE and ISS.

Efficacy Results – Primary Endpoint

The applicant has provided interim results for ARIEL2 using HRD classification as described above, based on central testing using the Foundation Medicine, Inc., HRD assay; however, these interim analyses do not form a part of the efficacy and safety evaluations incorporated in this marketing application. Efficacy results are presented in the ISE and ISS.

11.2.3. Study CO-338-010, "Study 10"

Trial Design and Endpoints

This clinical trial sponsored by the applicant is entitled, "A Phase 1/2, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Ovarian Cancer or Other Solid Tumor." The trial is ongoing; therefore, interim data are provided for this marketing application. The data analysis to support evaluations of safety and efficacy are presented in the integrated summaries of safety and efficacy, and are not themselves part of the statistical analysis plan of this trial as described in the protocol document. Data are presented for patients from part 1 and part 2A with a visit cutoff date of November 30, 2015. Data are not presented for patients from part 2B, which had just started accrual at the data cutoff date.

The primary objectives of this trial were to evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumors and to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) (part 1); to characterize the pharmacokinetic profile of rucaparib (part 1 and 3); and to evaluate the objective response rate (ORR) in patients with relapse, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer associated with a BRCA mutation (part 2).

Secondary endpoints include characterizing the food effect on the PK profile of rucaparib, evaluating the effect of rucaparib on the QT/QTc by ECG, continuing evaluation of safety and efficacy, and estimating antitumor activity, PFS, DOR, and OS. Exploratory objectives include evaluating relationships between PK

and QT/QTc, profiling circulating metabolites at steady state at RP2D, and exploring the association between genomic alterations in tumor tissue and clinical outcomes.

The first patient entered the trial on December 14, 2011. In part 1, patients were initially treated in a dose escalation evaluation period (cycle 1) and could then begin treatment with an optional treatment extension period (cycles 2+). Cohorts of patients in a standard 3+3 design received dose escalations of rucaparib ranging from 40 mg QD to 840 mg BID, for either one or two 21-day cycles. Dose-limiting toxicities were assessed until the MTD was determined. Once the RP2D was established, at 600 mg BID, an expansion cohort of phase 1 patients with solid tumors and gBRCAm was treated. The effect of food on rucaparib PK and profiling of rucaparib metabolites were also assessed in subsets of patients.

In part 2, the tolerability and efficacy of rucaparib 600 mg BID was assessed in (part 2A) patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a gBRCAm who had progressed after two to four prior regimens. This part used a Simon two-stage design to evaluate efficacy, with 21 patients treated in stage 1 and 20 patients treated in stage 2 after at least two responses in stage 1. Part 2B enrolled ovarian cancer patients with gBRCAm or somatic BRCAm (sBRCAm) who had been treated with three or four prior treatment regimens. Cycle length was 21 days.

Part 3 of the trial evaluated the PK of 600 mg oral rucaparib in patients with any advanced solid tumor with evidence of gBRCAm or sBRCAm after a single administration on two separate dates (day -7 and day 1) for assessing the effect of food on PK, then continued with BID dosing at 600 mg on 21-day cycles.

Efficacy in this trial was assessed by confirmed tumor response using RECIST v. 1.1 as measured by the investigator, primarily in computed tomography of the chest, abdomen, and pelvis. The applicant also used tumor markers, including cancer antigen-125 (CA-125) to assess efficacy. Efficacy evaluations include ORR, (RECIST v1.1 by investigator) and DOR. In the current application, planned efficacy analyses for Study 10 that are not included are: PFS, CA-125 response rate by GCIG criteria, evaluation of antitumor activity, and overall survival. A total of 42 patients were included from part 2A of Study 10 in the efficacy population for this application, based on meeting the required baseline characteristics, and analyzed in the ISE. Safety was assessed in all patients, including monitoring AEs, physical examination, clinical laboratory examinations, and ECGs. AEs were graded according to NCI CTCAE v4.03 and classified according to MedDRA version 18.1. Incidences of all treatment-emergent AEs were summarized by preferred term and CTCAE grade and seriousness, as well as AEs leading to dose modification.

FDA's review of efficacy is limited to analysis of ORR and duration of response for the efficacy population in this single-arm application as defined in NDA209115, and is supported by evaluation of duration of response in the efficacy population. As noted in section 11.2.3 there were 42 patients from Study 10 that were included in the efficacy population for this application, and an additional 33 that formed the safety population, as discussed in the ISE and ISS, below.

Inclusion Criteria

Patients who fulfilled all of the following criteria were eligible for enrollment. Unless otherwise specified, the criteria below apply to patients enrolling in all 3 parts of the trial.

1. Understood and voluntarily signed an IRB/IEC-approved ICF prior to any trial-specific evaluation.
2. Were ≥ 18 years of age at the time the ICF was signed.
3. Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Had a life expectancy of at least 3 months.
5. Had adequate organ function, confirmed by the following laboratory values obtained ≤ 14 days prior to the first dose of rucaparib:
   a. Bone Marrow Function
      i. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
      ii. Platelets > 100×10^9/L
      iii. Hemoglobin ≥ 9 g/dL
   b. Hepatic Function
      i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN
      ii. Bilirubin ≤ 1.5 × ULN (< 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome)
      iii. Serum albumin ≥ 30 g/L (3.0 g/dL) (Part 2B)
   c. Renal Function
      i. Serum creatinine ≤ 1.5 × ULN

Patients enrolled into Part 1 (Phase 1 portion) also met the following inclusion criteria:

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

All patients enrolled into Part 2 (Phase 2 portion in OC patients) also met the following inclusion criteria:

10. Had a known deleterious BRCA mutation (germline for Part 2A, germline or somatic for Part 2B), as determined by a local laboratory that has received an international or country-specific quality standards certification.
11. Had evidence of measurable disease as defined by RECIST v1.1.
12. Had sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue available for planned analyses; cytospin blocks from ascites were not acceptable (retrospectively for Part 2A).
13. Archival tissue from the most recently collected biopsy or debulking surgery should have be provided, if available. Otherwise, the next oldest tissue collected should have been reviewed until a suitable sample had been provided (at least 20% tumor content with a minimum of 80% nucleated cellular content).

Additional inclusion criteria for patients enrolled into Part 2A (Phase 2 portion in OC)included:

14. Had a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer.
    - For mixed histology, > 50% of the primary tumor must have been confirmed to be high-grade serous or endometrioid upon re-review by local pathology.
15. Had received at least 2, but no more than 4, prior chemotherapy regimens and had relapsed as confirmed by radiologic assessment.
    - Last treatment received must have been platinum-based regimen to which patient must have been sensitive (ie, disease progression occurred at least 6 months after last dose of platinum was administered).
    - A maximum of 1 non-platinum regimen may have been administered. For patients who received 4 prior regimens, 1 regimen must have been a non-platinum.
    - Prior continuous or switch maintenance treatment was permitted (hormonal treatment was permitted following the last platinum regimen with advance approval from the sponsor).

Additional inclusion criteria for patients enrolled into Part 2B (Phase 2 portion in OC) included:

16. Had a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

17. Had received at least 3, but no more than 4, prior chemotherapy regimens and had relapsed disease confirmed by radiologic assessment.
    - Hormonal agents (eg, tamoxifen, letrozole, etc.), anti-angiogenic agents (eg, bevacizumab, pazopanib, cediranib, nintedanib, trebananib, etc.), and other non-chemotherapy agents administered as single agent treatment were not counted as a chemotherapy regimen for the purpose of determining patient eligibility.
    - Agents administered in the maintenance setting were not counted as a separate regimen.
18. Had a documented treatment-free interval (TFI) of ≥ 6 months following the first chemotherapy regimen received. (TFI was determined from the last dose administered as part of primary treatment regimen and not from the last dose of any agent administered in the maintenance setting).

Patients enrolled into Part 3 (Phase 2 PK portion in patients with any advanced solid tumor) must have also met the following inclusion criteria:

19. Had an advanced solid tumor (inclusive of lymphoma).
20. Had a known deleterious BRCA mutation (germline or somatic), as determined by a local laboratory that has received an international or country-specific, quality standards certification.
21. Had evidence of measurable disease as defined by RECIST v1.1.
22. Had been willing and able to fast, and to eat a high-fat breakfast on Day -7 or Day 1 of the study.
23. Had sufficient archival FFPE tumor tissue available for planned analyses; cytospin blocks from ascites were not acceptable.
    - Archival tissue from the most recently collected biopsy or debulking surgery should have been provided, if available. Otherwise, the next oldest tissue collected should have been reviewed until a suitable sample was provided (at least 20% tumor content with a minimum of 80% nucleated cellular content).

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study. Unless otherwise specified, the criteria below apply to patients enrolling in all 3 parts of the study:

1. Had an active second malignancy, ie, patient known to have potentially fatal cancer present for which she/he may have currently been (but not necessarily) receiving treatment.
    a. Patients with a history of malignancy that had been completely treated, with no evidence of that cancer currently, were permitted to enroll in the trial provided all

chemotherapy had been completed > 6 months prior and/or any bone marrow transplant (BMT) > 2 years prior to first dose of rucaparib.

2. Had received prior treatment with any PARPi (Part 1 and Part 2). Part 3 patients were permitted to have had previous PARPi, if the following conditions were met:
   a. PARPi was not the most recent treatment; and
   b. PARPi was discontinued > 6 months before first planned dose of rucaparib.
   c. In all study parts, patients who had previously received iniparib were eligible.
3. Had untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases were eligible provided they had been clinically stable for at least 4 weeks.
4. (Criterion removed in Amendment 5):

   Had impaired cardiac function or clinically significant cardiac disease, including any of the following:
   a. Unstable angina pectoris ≤ 3 months prior to first scheduled dose of rucaparib;
   b. Acute myocardial infarction ≤ 3 months prior to first scheduled dose of rucaparib.
5. Had known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C.
6. Had received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to first dose of rucaparib and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1 (ongoing Grade 2 non-hematologic toxicity related to most recent treatment regimen was permitted with prior advanced approval from sponsor).
7. Had pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would have, in the opinion of the investigator, interfered with absorption of rucaparib.
8. Had received administration of strong cytochrome P450 (CYP1A2 or CYP3A4) inhibitors ≤ 7 days prior to first scheduled dose of rucaparib.
9. Had undergone a non-study related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of rucaparib; in all cases, the patient must have been sufficiently recovered and stable before treatment administration.
10. Were females who were pregnant or breastfeeding.
11. For fertile patients (female able to become pregnant or male able to father a child), had refused to use effective contraception during the period of the trial and for 6 months after the last dose of oral rucaparib.
12. Had presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse; psychiatric disturbance; or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism).

13. Had presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.
14. (Criterion removed in Amendment 5):

    Had a history of clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QTcF) > 450 msec (males) or > 470 msec (females), PR interval > 240 msec, or QRS complex > 110 msec.

Patients enrolled into Part 1 (Phase 1 portion) of the study were also excluded from participation if any of the following criteria applied:

15. Had a family history of long QT syndrome;
16. Had an implantable pacemaker or implantable cardioverter defibrillator; and
17. Required treatment with any medication known to produce QT prolongation, with the exception of necessary antiemetic medications.

Patients enrolled into Part 2B (Phase 2 OC portion were also excluded from participation if any of the following criteria applied:

18. Were hospitalized for bowel obstruction within 3 months prior to enrollment.

Dose Modification and Management Algorithms

Dose escalation

All patients except those in the food-effect PK portions of Part 1 and Part 3 received oral rucaparib either on an empty stomach or with food. Tablets were to be swallowed whole with 8 oz (240 mL) of room temperature water. Patients on a BID dosing schedule were to take rucaparib doses as close to 12 hours apart as possible. Doses that were not taken within 4 hours of the scheduled time for the BID schedule were considered missed; patients were to resume taking rucaparib with their next scheduled dose and not to make up for any missed or vomited doses.

Part 1 (Phase 1 Portion)

In each dose-escalation cohort, patients ingested rucaparib once or twice daily through day 21 of cycle 1. Patients who entered the optional treatment extension period continued treatment with rucaparib starting on Day 1 of Cycle 2.

For the first dose-escalation level (cohort 1), 3 patients were enrolled at a starting dose of 40 mg oral rucaparib. Enrollment, treatment, and evaluation of each patient occurred in parallel. The occurrence DLTs were used to determine whether the dose level was escalated in subsequent cohorts.

DLTs were defined as any subsequent events (Table XX) that occurred during cycle 1 and were assessed by the investigator as related to rucaparib. Where applicable, events were classified according to NCI CTCAE Version 4.03.

- ANC < 0.5×10^9/L >5 days duration or febrile neutropenia (ie, fever > 38.3°C with ANC < 1.0×10^9/L);

- Platelets < 25×10^9/L or platelets < 50×10^9/L with bleeding requiring a platelet transfusion;

- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated); or

- Any nonhematological AE CTCAE Grade 3 or greater (except alopecia and nausea, vomiting, and diarrhea if well-controlled by systemic medication).

The MTD was defined as the maximum daily oral dose at which < 33% of patients experienced a DLT during Cycle 1. If a DLT was observed in 1 of 3 patients, then 3 additional patients were enrolled at the same dose level. Dose escalation continued until at least 2 of the 3 to 6 patients treated at a dose level experienced a DLT. The next lower dose was then considered the MTD. Alternatively, if the dose between the MTD and the maximally delivered dose was significant (such as 100%), then a more modestly de-escalated dose was explored (eg, 20% to 50%).

Dose escalation for Part 1 of the study is described in Table 6

Table 6 Dose Escalation Plan for Part 1

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

600 mg BID	1200 mg	25% (Actual)
840 mg BID	1680 mg	40% (Actual)

Source: Study 10 CSR

Part 2 and Part 3 (Phase 2 Portion)

Patients enrolled in Part 2 or Part 3 ingested oral rucaparib (21-day cycles) at 600 mg BID, the RP2D determined in Part 1.

Dose modification

Rucaparib dose modifications for Phase 1 and Phase 2 are described below. Changes to dose modification criteria implemented in amendments to the protocol are presented below.

Phase 1 (part 1)

No dose reductions were permitted in Cycle 1 in Part 1 of the study. After Cycle 1, dose reductions were permitted if a patient experienced a DLT in Cycle 1. In this case, the investigator may have:

- Continued treating the patient at the next lower dose level evaluated (oral rucaparib was not to be reduced below 40 mg) if the investigator expected clinical benefit from further treatment with rucaparib, the toxicity was manageable, and the investigator and the sponsor's medical monitor (or designee) agreed; or
- Discontinued the patient from rucaparib treatment and the study.

During the optional treatment extension period in part 1, the dose of oral rucaparib may have been reduced to the next lower dose level evaluated, if any of the following were observed:

- Grade 3 or 4 hematologic toxicity;
- Grade 3 or 4 nonhematologic toxicity (except for alopecia, and nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines);
- Continued rucaparib administration was permitted after observation of grade 3 elevations of ALT/AST provided bilirubin was < ULN, alkaline phosphatase (ALP) was < 3x ULN, and there were no other signs of liver dysfunction. Rucaparib was to be held if ALT/AST did not decline within 2 weeks or continued to rise. Rucaparib treatment could resume at either the current dose or reduced dose upon resolution to ≤ grade 2 ALT/AST.
- In addition, and at the discretion of the investigator, the dose of rucaparib may have been held and/or reduced for grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Treatment with rucaparib was to be held until the toxicity resolved to ≤ grade 2. Dosing could then be resumed at either the same dose or the next lower dose level evaluated, per investigator discretion. If treatment was resumed at the same dose and the patient experienced the same toxicity, the dose was to be reduced following resolution of the event. If the patient continued to experience toxicity, a second and third dose reduction to a previously evaluated lower dose were permitted. Up to 3 dose reduction steps were allowed. If a patient continued to experience toxicity after 3 dose reduction steps, or if dosing with rucaparib was interrupted for > 14 consecutive days due to toxicity, treatment was to be discontinued, unless otherwise agreed between the investigator and the sponsor.

A new cycle of treatment could begin if:

- ANC ≥ 1.0 x 10^9/L;
- Platelet count ≥ 75.0 x 10^9/L; and
- Non-hematologic toxicities 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).

Monitoring Plan

A sample monitoring plan from Study 10 is shown in Table 10.

Table 7 Schedule of Events – Part 1: All Cohorts Except Food-effect Evaluation

Procedure [a]	Screening	Dose-Escalation Evaluation			Optional Treatment-	End of Treatment (after Last Dose)	Follow-up (28 [± 3] Days after Last Dose)
		Cy			Cycles 2+		
	Day -30 to Day -	Day -1	Day 1 [b]	Days 8, 15, & 22	Day 1 [c]		
Informed Consent	X						
Medical/Oncology History	X						
Physical Examination	X		X	X [d]	X	X	
Height	X						
Weight	X		X	X	X	X	
ECOG Performance Status	X		X		X	X	
Vital Signs [e]	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	
12-lead ECG (in Triplicate) [f]	X	X	X [b]	X [b,i]	X	X	
ECHO or MUGA Scan [j]	X						
Hematology [k]	X [l]		X	X	X	X	
Serum Chemistry [m]	X [l]		X	X	X	X	
Serum Pregnancy Test	X [n]					X	
Urinalysis [o]	X						
Tumor Markers (optional) [p]	(X)		(X)		(X)	(X)	
Tumor Scans [q]	X				X	X	

Tumor Samples (optional) [s]	(X)					(X)	
Adverse Events [t]	X	X	X	X	X	X	X
Plasma PK Samples			X [u]	X [u,v]	X [v]		
Duplicate Set of Plasma PK Samples for Metabolite			(X) [w]	(X) [i,x]			
Oral Rucaparib Dispensation/Administration			X	X	X		

Source: Study 10 CSR

AE = adverse event, ALT = alanine aminotransferase, ALP = alkaline phosphatase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CR = complete response, CT = computed tomography, ECG = electrocardiogram, EOS = end of study, hCG = human chorionic gonadotropin, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response, SAE = serious adverse event

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

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

c = Cycle 2, Day 1 assessments were not repeated if the visit was the same day as Cycle 1, Day 22 or no more than 7 days later. Note:theplasmaPK samplewas collectedonDay22ofCycle1only.NoadditionalsamplewascollectedifaseparateCycle2,Day1Visitwasrequired.

d = Limited/targeted physical exam was performed on Days 8 and 15 of Cycle 1.

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

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

g = At a time point equivalent to the estimated postdose Tmax of oral rucaparib administered on the following day. This ECG was time-matched to the 12-lead ECG taken on the following day at estimated Tmax [2 hrs after administration] following oral dosing with rucaparib.

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

i = Day 15 and Day 22 only.

j = Repeated during treatment period as clinically indicated.

k = Included hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood was analyzed by a local laboratory and results were reviewed by the investigator prior to dosing with rucaparib.

l = Performed ≤14 days prior to the first dose of rucaparib.

m = Included total protein, albumin, creatinine, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO , calcium, and phosphorus. Blood was analyzed by a local laboratory.

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

o = Included dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings were abnormal, performed microscopic evaluation to assess abnormal findings.

p = Optional: tumor markers appropriate to a patient's cancer diagnosis were measured by a local laboratory.

q = Tumor assessments consisted of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) were performed if required. The same methods used to detect lesions at baseline were used to follow the same lesions throughout the clinical study.
r = Tumor scans were performed within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10. If initial CR or PR was noted at Cycle 7 or beyond, confirmatory scans were performed 4–6 weeks later.
s = Tumor tissue samples were optional. The patient must have provided consent to provide archival and/or fresh tumor tissue samples at screening and at time of disease progression/treatment discontinuation. For archival tissue, the most recent sample collected prior to treatment was to be provided.
t = AEs were recorded from time of signing of informed consent through 28 days after last dose of rucaparib. Ongoing SAEs were followed to resolution.
u = PK samples were collected predose (any time on Day 1; 5-10 min prior to dosing on Day 15) and at 15 (± 2) min, 30 (± 3) min, 1 hr (± 5 min), 1.5 hrs (± 5 min),
2.5 hrs (± 5 min), 4 hrs (± 15 min), 6 hrs (± 15 min), 8 hrs (± 15 min), 10 hr (± 30 min), and 24 hrs (± 30 min) postdose on Days 1 and 15 of Cycle 1.
v = PK sample was collected any time prior to dosing on Days 8 and 22 of Cycle 1, and on Day 1 of Cycles 3-9
w = PK sample for metabolite profiling on Day 1 was predose only.
x = Duplicate set of PK samples was collected from first 3 patients enrolled into the RP2D Expansion cohort only. PK samples were collected predose (5–10 min prior to dosing) and at 15 (± 2) min, 30 (± 3) min, 1 hr (± 5 min), 1.5 hrs (± 5 min), 2.5 hrs (± 5 min), 4 hrs (± 15 min), 6 hrs (± 15 min), 8 hrs (± 15 min), 10 hrs (± 30 min), and 24 hrs (± 30 min) postdose.

Source: Table 6, page 44, Protocol CO-338-010, Amendment 6, from CSR Appendix 16.1, dated May 24, 2016

Adverse Event Collection

Safety was assessed by evaluating clinical laboratory and ECG abnormalities, and changes in physical examinations, and by monitoring the incidence, severity, and relationship of treatment emergent adverse events (TEAEs). Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.]

Statistical Analysis Plan

Statistics for Study 10 were primarily descriptive, and included summary tables of quantitative variables by frequency and percentages with additional descriptive statistics, while categorical variables were presented as frequencies and percentages. Kaplan-Meier methodology was used to summarize time-to-event variables. There were no imputations for missing data. The primary efficacy endpoint was evaluated in the efficacy-evaluable population in part 2A of the trial: ORR defined as best confirmed response as assessed by the investigator per RECIST v1.1, and is summarized using frequencies and percentages. Secondary endpoints were further explored to evaluate DOR.

The efficacy evaluable population for Study 10 consists of 42 patients who met eligibility criteria, received at least one dose of rucaparib, had measurable disease at baseline, and had at least 1 post-baseline assessment. These patients are included in the integrated summary of efficacy. The safety population for Study 10 includes all patients who had at least one dose of study drug.

Sample Size Considerations

The Applicant planned to enroll 140 patients in this study. Part 1 was planned to enroll 50-60 patients based on an estimate of 6-12 patients per dose escalation cohort, with a minimum of 3 patients per cohort, and a dose expansion at the RP2D of up to 15 patients. In Part 2A, up to 41 evaluable patients with platinum-sensitive, relapsed, high-grade ovarian cancer (including serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer) associated with a gBRCA mutation, with an expected ORR of 20%. The trial used a Simon 2-stage design to evaluate efficacy, where 21 patients were assigned to stage 1, and if ≥ 2 responses, an additional 20 patients were to be treated in stage 2. This model included a 5% probability of accepting a poor drug, with a 90% probability of accepting a good drug, with ORR cutoffs of 5% and 20%.

Protocol Amendments

Key Protocol amendments to Study 10 are summarized in Table 11.

Table 8 Summary of Key Protocol Amendments and Addenda

Number	Date	Details of Amendment / *Rationale*
Amendment 1	12 January 2012	• Exclusion criteria were revised to apply exclusion for history of clinically significant abnormal ECG to patients in both Parts 1 and 2 of the trial. Previously this exclusion had only applied to patients enrolling into Part 1 of the study. *This change was implemented for patient safety*. • Withdrawal criteria were revised to include absolute QTc measurement > 500 msec as reason for withdrawal. *This change was implemented for patient safety*.
Amendment 2	23 April 2012	• The trial design was revised to include an ovarian cancer arm in Part 2 of the study, and the trial size was adjusted accordingly. • (b) (4) • The inclusion criteria for Part 2 patients were revised to note that gBRCA testing must have been conducted in a laboratory that is internationally or nationally accredited. • Inclusion criteria were added for ovarian cancer patients in Part 2. • An optional collection of a fresh or archival tumor tissue sample was added for patients who consented to provide a biopsy sample. • Re-treatment criteria were added to guide dosing for Cycle 2 and beyond.
Amendment 3	2 October 2012	• The dose escalation plan was revised to included evaluation of BID, and possibly TID dosing. • The number of cohorts was increased to reflect ongoing dose escalation and evaluation of BID and TID dosing. • The study population for the RP2D expansion cohort was revised to include patients with a solid tumor and a deleterious gBRCA mutation, and the size was increased to up to 15 patients. • Health-related quality of life (HRQoL) assessment was added to Part 2 of the trial. • Eligibility criteria were revised to: o Require patients in the RP2D expansion cohort to have a deleterious gBRCA mutation. o Allow ovarian cancer patients in Part 2 to have received prior treatment with a non-platinum regimen. • The option for intrapatient dose escalation was added to Part 1 of the trial. • The End-of-Study Visit was split into 2 visits. • The concomitant medications section was revised to remove the restriction for concomitant low-dose anticoagulants. • Safety information for the A4991014 trial was updated to reflect the most current information included in the Investigator's Brochure.

Amendment 4	27 November 2013	• The RP2D was determined to be 600 mg BID based on safety, PK, and efficacy data from the Phase 1 portion. • The dose modification criteria were revised to allow for additional rucaparib dose reduction steps. • The re-treatment criterion for ANC was changed from 1.5 to 1.0 x 10^9/L Changes to Part 2 (Phase 2) • (b) (4) • The inclusion and exclusion criteria were revised to provide additional detail regarding the patient population The ovarian cancer patient population inclusion criteria were modified *to be consistent with the other Phase 2 and Phase 3 ovarian cancer studies being conducted by the sponsor*.
Amendment 5	2 February 2015	• A third part (Part 3) was added to the study to further evaluate the PK of, and the effect of food on, higher dose strength tablets at the RP2D in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation (germline or somatic). • The trial objectives and endpoints were revised and clarified: o The following exploratory endpoint was changed to a secondary objective and corresponding endpoint: To assess progression-free survival (PFS) in the platinum-sensitive OC population (Part 2 only). o The following secondary objective (and corresponding endpoint) was modified to include Part 3: To evaluate antitumor activity of oral rucaparib in various solid tumors (Part 1 and Part 3 only).
Amendment 6	27 April 2015	• An additional cohort of patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with evidence of a deleterious BRCA mutation (germline or somatic) who have received at least 3, but no more than 4, prior chemotherapy regimens was included in the Phase 2 part of the trial. Initial Part 2 became Part 2A, and the new cohort of patients was enrolled into Part 2B. • A secondary endpoint of overall survival was added for Part 2B.

Source: Study 10 Clinical Study Report, Appendix 1.

11.1.4. **Study Results** for Study 10

Compliance with Good Clinical Practices

The trial was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the U.S. Code of Federal Regulations (CFR, Title 21 CFR § 50, 56, and 312), International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) 1996, and the Declaration of Helsinki (World Medical Association 2013).

In addition, the trial was conducted in accordance with the protocol and applicable local regulatory requirements and laws. Agreement to adhere to the protocol was indicated by investigators signing and returning the protocol signature page and providing a copy of their curricula vitae (CVs) to the applicant (Clovis Oncology, Inc.).

Investigators were made aware that regulatory authorities and sponsor representatives could inspect study documentation and patient records at any time. Each investigator was responsible for preparing an ICF, based on the template ICF form provided by the sponsor, and a privacy authorization (United States [U.S.] only, template provided by the sponsor). The ICF was in compliance with ICH GCP, the Declaration of Helsinki, local regulatory requirements, and legal requirements. The ICF used in this study, and any changes made during the course of the study, were approved by both the IRB/IEC and the sponsor before use. All patients were informed of the aims, methods, objectives, and potential hazards of the study, and were given sufficient time and opportunity to inquire about any specific aspects before providing written consent to participate. A signed ICF was obtained from each patient prior to enrollment.

Financial Disclosure

The applicant submitted a list of investigators (NDA module 1.3.4) and forms 3454 that certify that most investigators participating in the trial had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the studies. Financial disclosures and forms 3455 were provided for two investigators. (b) (6) is listed as having received > $25,000 for sponsorship of a research project entitled, (b) (6) (b) (6) (b) (6)

Reviewer Comment:

(b) (6)

Patient Disposition

The disposition of all patients included in the interim CSR safety population for Study 10 is presented in Table 12. The safety population for the CSR included all patients, regardless of baseline characteristics, who received at least 1 dose of rucaparib. Note that this is not identical to the safety population contributed from this study to the integrated summary of safety for the application.

Table 9 Disposition of All Patients in the Safety Population Study CO-338-010

	Safety Population N=124 n (%)
End of treatment status	
Ongoing	22(18)
Discontinued	102 (82)
Primary discontinuation reason	
Progressive disease	70 (56)
Adverse event	9 (7)
Death	0
Physician decision	2 (2)
Protocol deviation	1 (1)
Clinical progression	17 (14)
Other*	3 (2)

Source:

*One physician decision was based on increase in CA-125

**The three patients described as "other" were removed from study drug treatment for elevation of CA-125.

Protocol Violations/Deviations

There were 9 major protocol deviations in a total of 9 patients. There were 4 major violations related to screening assessments: 1 patient in Part 3 with prostate cancer had no measurable disease per RECIST v1.1; one patient in Part 1 had a history of clinically significant abnormal 12-lead ECG; 1 patient in Part 2A had a history of prior malignancy (thyroid cancer); and 1 patient in Part 2A had clear cell ovarian cancer associated with a gBRCA mutation, rather than the protocol-specified serous or endometrioid ovarian cancer. There were 5 major on-study violations: 1 patient in Part 1 was non-compliant with the contraception method; and 4 patients in Part 1 received prohibited concomitant medications associated with QTc prolongation (2 patients received levofloxacin, and 1 patient each received either methadone or metaclopromide). The restriction on concomitant use of metoclopramide was later removed.

Reviewer Comment:
These deviations were deemed to not significantly impact the integrity of the study and the collection of data of sufficient quality to support the safety and efficacy analyses presented in the integrated summaries of efficacy and safety.

Table of Demographic Characteristics

Data for this interim clinical study report (CSR) include 124 patients recruited from 13 sites in the United States (U.S.), United Kingdom (U.K.), Spain, Israel, and Canada. The trial is currently ongoing at 7 sites in the U.S., U.K., and Israel. Of patients in the application, 75 patients in the safety population and 42 patients in the efficacy population were from this trial. The demographics and baseline characteristics for this trial are aggregated with patients from the other two studies and presented in the ISS and ISE sections, below.

Efficacy Results - Primary Endpoint

The applicant has provided interim results for Study 10 based on an efficacy population of 40 patients; however, these interim analyses do not form a part of the efficacy and safety evaluations incorporated in this marketing application that will be discussed below in the integrated summary of efficacy and the integrated summary of safety.]

11.2.5. Study CO-338-023, RUCAPANC

Trial Design and Endpoints

This clinical trial conducted by the applicant is entitled "A Phase 2, Open-Label Study of Rucaparib in Patients with Pancreatic Cancer and a Known Deleterious *BRCA* Mutation." The data analysis to support evaluation of safety is presented in the integrated summaries of safety and is not part of the statistical analysis plan of this trial as described in the protocol document. (b) (4)

There were no safety concerns for rucaparib observed by the DMC, so patients in the consenting/ screening process were allowed to complete screening, and enroll in the trial. Total enrollment was 19 patients. The first patient entered the trial on June 12, 2014, and the last patient was entered February 18, 2015. Data are presented for the 19 patients enrolled with a visit cutoff date of April 11, 2016 as per the updated safety report.

The primary objective of the trial was to evaluate the activity of rucaparib in patients with pancreatic adenocarcinoma associated with a deleterious breast cancer gene (*BRCA*) mutation.

The secondary objectives of the trial were to evaluate activity by assessment of response as determined by independent radiology review, assess duration of response (DOR), evaluate progression-free survival (PFS), evaluate overall survival (OS) benefit, evaluate the safety and tolerability of rucaparib, and evaluate steady state trough level pharmacokinetics (PK).

This was an open-label, single arm trial of rucaparib in patients with locally advanced or metastatic pancreatic cancer and a known deleterious germline or somatic *BRCA* mutation. Treatment with rucaparib occurred in continuous 28-day cycles with patients assessed for disease status per RECIST v1.1) after every second cycle of treatment. Patients were monitored for safety during the trial and continued to receive rucaparib until disease progression or other reason for treatment discontinuation as described in the protocol. All patients had a 28-day follow-up period for adverse events (AEs) following the last dose of rucaparib. After the 28-day follow-up visit, patients were followed for survival every 4 weeks until death, loss to follow-up, withdrawal of consent, or study closure. Overall, patients received between 1 and 13 cycles of rucaparib as of the visit data cut-off; however, 3 patients were continuing treatment.

FDA's review of safety includes data from this study in the analyses of death only, section 11.5.6 Safety Results; Deaths. All other safety analyses are conducted on the safety population of ovarian cancer patients only.

Inclusion and Exclusion Criteria

Eligible patients who had provided written informed consent were aged ≥ 18 years with histologically or cytologically-confirmed diagnosis of pancreatic cancer (including ductal adenocarcinoma and related subtypes, but not endocrine or neuroendocrine tumors), measurable disease by RECIST v1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy > 8 weeks, and adequate hematological and biological function. Patients must also have had documented deleterious or suspected deleterious (or equivalent interpretation) *BRCA* mutation (germline or somatic) as assessed by a local laboratory and had relapsed or progressive disease having received at least one, but no more than two, chemotherapy-based regimens for locally advanced or metastatic disease. Patients were excluded if they had another active cancer, prior treatment with a PARP inhibitor (except iniparib), clinical evidence of malabsorption and/or any other gastrointestinal disorder or defect that would interfere with the absorption of rucaparib, symptomatic and/ or untreated central nervous system metastases, or received pancreatic cancer treatment within 14 days prior to the first dose of rucaparib.

Dose Modifications

The dose of rucaparib was to be held for Grade 3 or 4 hematologic toxicity, Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled), and at the discretion of the investigator, held and/or reduced for Grade 2 toxicity not adequately controlled. Treatment was to be held until the toxicity resolved to CTCAE Grade 2 or less. Dose reduction steps were

outlined and dose re-escalation upon resolution of toxicity to CTCAE Grade 1 or less was permitted upon agreement between investigator and sponsor.

Adverse Event Collection
The safety assessments performed included monitoring of AEs, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs, and 12-lead ECG.

Statistical Analysis Plan
The primary efficacy endpoint of ORR was analyzed as the proportion of patients with a best confirmed response of CR or PR as assessed by the investigator using RECIST v1.1 and was summarized with frequencies and percentages. In addition, DOR was defined as the number of days from the date that a response was first recorded until the first documented date of progressive disease (PD). Duration of response was only reported for confirmed responses per RECIST v1.1 and summarized as a time-to-event variable. For patients who continued treatment post-progression, the first date of progression was used for the analysis. Patients with a response who did not have PD were censored at the last post-baseline scan date.

Adverse events were classified using MedDRA Version 18.1. The severity of the toxicities were graded according to the CTCAE Version 4.03 whenever possible.

Reviewer comment:
(b) (4)
. This FDA review for rucaparib used data from this trial only for the safety analyses for deaths, *section 11.5.6 Safety Results,* (b) (4)

11.3 Integrated Review of Effectiveness

11.3.1. Assessment of Efficacy Across Trials

Introduction and Primary Endpoints

The applicant submitted an NDA for accelerated marketing approval for rucaparib based on efficacy and safety data from patients enrolled in five separate trial sections from two international, multi-center, single-arm, open-label clinical trials. Studies CO-338-010 (Study 10) and CO-338-017 (ARIEL2) are described in detail above. The sponsor's proposed indication was:

> Rubraca is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline BRCA and

somatic BRCA mutations (as detected by an FDA approved test), and who have been treated with two or more chemotherapies.

This integrated review of efficacy addresses efficacy data from a group of patients from Study 10 and ARIEL2 that were treated with 600mg twice daily with rucaparib. The primary rucaparib efficacy population is comprised of 106 patients with ovarian cancer harboring deleterious BRCA mutations who had undergone treatment with two or more prior platinum-containing chemotherapy regimens. Efficacy evaluations for this application are based on pooling patient data from these two ongoing trials, with cutoff dates for the datasets as detailed in Table 13.

The data provided by the applicant allowed replication of the primary efficacy and key secondary results. The submitted SAPs had provisions for the primary analysis for each of the individual studies. This NDA is based on data from two different trials, and the analyses for the combined studies were agreed upon in a pre-NDA meeting. Standard SAS procedures were used for performing analyses.

Table 10 Summary of Efficacy Data Cutoff Dates

Study	SCE Includes Data from Patients Enrolled By:	Includes All Visits Until:
Study 10 Part 2A	Enrollment completed April 2015; all enrolled patients included	November 30, 2015
ARIEL2 Part 1	Enrollment completed in October 2014; all enrolled tBRCAm patients included	February 29, 2016
ARIEL2 Part 2	October 1, 2015 (enrollment ongoing at data cutoff)	February 29, 2016

Source: Summary of Clinical Efficacy, NDA 209115

For the efficacy analysis for NDA 209115, the primary rucaparib efficacy population is patients treated in Study 10 or ARIEL2 who met the following criteria:

1. Had a diagnosis of ovarian cancer (inclusive of primary peritoneal and fallopian tube cancer);

2. Received ≥ 2 prior chemotherapy regimens, including at least 2 platinum-based regimens;

3. Had a deleterious gBRCA or sBRCA mutation as detected by the CTA *or* a local laboratory test

4. Were enrolled in a Study 10 or ARIEL2 study portion where ORR by RECIST Version 1.1 was the primary or a key secondary efficacy endpoint; and

5. Received at least 1 dose of rucaparib (600 mg).

The population in the primary efficacy analysis includes:

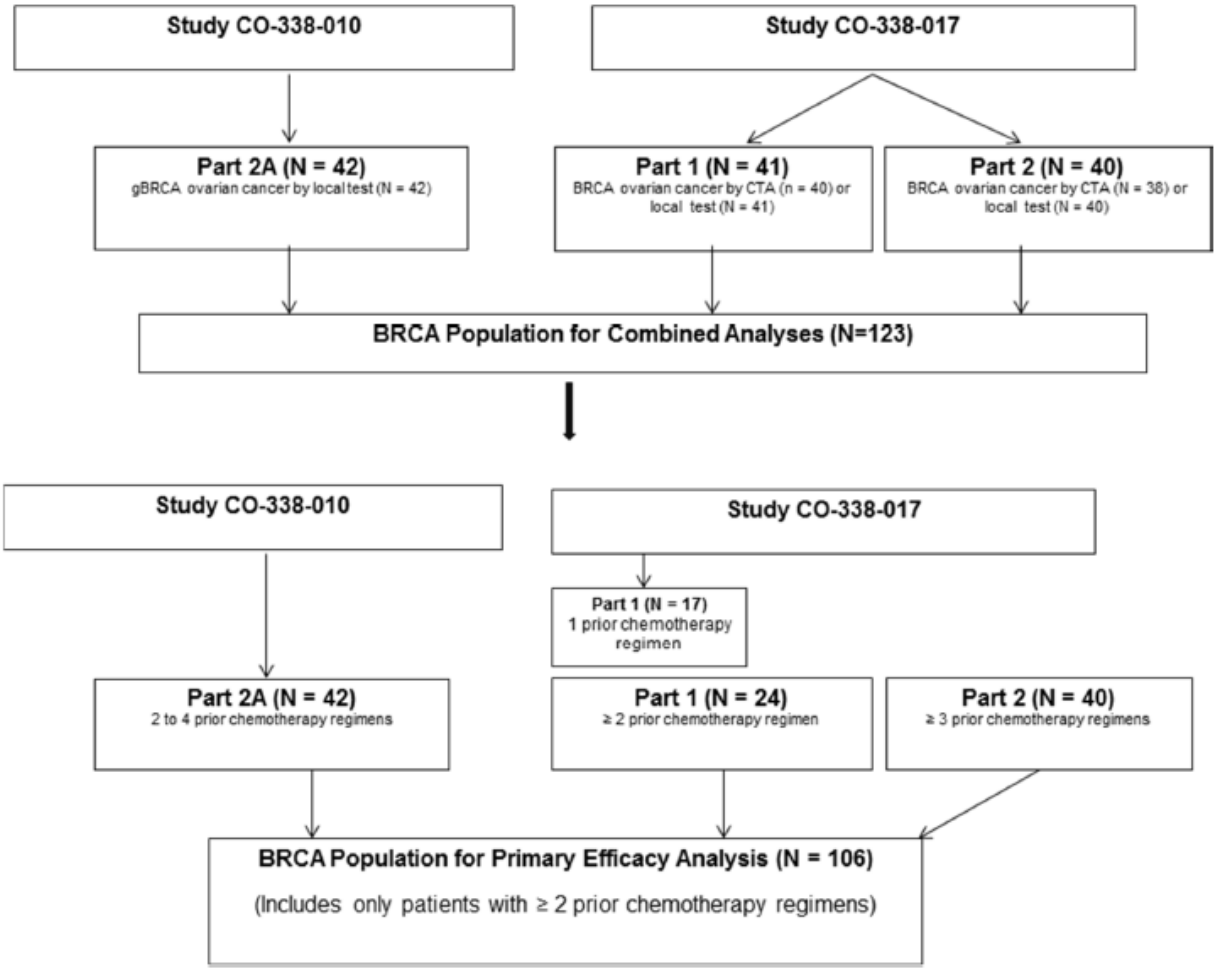
- All patients in Study 10 Part 2A (N = 42). All patients enrolled into Study 10 Part 2A were required to have a deleterious gBRCA mutation as identified by a local laboratory test and had received 2-4 prior treatment regimens. All patients treated had received at least 2 platinum-based regimens.

- Twenty-four patients in ARIEL2 Part 1. Overall, a total of 41 patients met the definition for harboring a deleterious BRCA mutation by either the CTA or a local laboratory result. Of these, 24 patients had received ≥ 2 prior chemotherapy regimens (including at least 2 platinum-based regimens).

- Forty patients in ARIEL2 Part 2. A total of 40 patients met the definition for harboring a deleterious BRCA mutation by either the CTA or a local laboratory result. All 40 patients received 3-4 prior chemotherapy regimens, including at least 2 prior platinum-based regimens.

The breakdown of patients included in the efficacy population is described in the consort diagram in Figure 1 below.

Figure 1: Flow Diagram of Patients with tBRCAm Ovarian Cancer After ≥ 2 Lines of Platinum-Based Treatment Regimens Incorporated into Primary Efficacy Population



Source:CSR

Endpoints

The primary efficacy analysis for this population of patients is the confirmed objective response rate (ORR) as assessed by the investigator according to RECIST v1.1; specifically, the ORR is the proportion of patients with a confirmed complete response (CR) or partial response (PR) on subsequent tumor measurement at least 28 days after first response documentation. Supportive efficacy analysis of the primary ORR endpoint was performed by independent radiology review (IRR) (b) (4)

Duration of response (DOR) as determined by investigator assessment is a key secondary response measure evaluated in this application, and was supported by analysis of DOR per IRR assessment. These findings are supportive data for objective response rates seen in patients.

Statistical Analysis Plan

Statistical analyses for this application were performed on a population derived from two ongoing phase 1/2 clinical trials. The study population, sample size, statistical considerations, and efficacy endpoints were discussed during meetings between FDA and the applicant, and an agreement was reached.

Data Quality and Integrity: Applicant's Assurance

The individual trials that contributed patient data to the safety population each had its own data quality and integrity assurance statements as described in sections 7.2. The data submitted for evaluation in this application include eCRFs, SDTM, and ADaM datasets for each of the contributing trials, as well as ADaM datasets derived directly from those trial datasets. The data presented were audited for consistency and found to be concordant.

Data Quality and Integrity—Reviewers' Assessment

Data were audited beginning with the electronic case report form (eCRF), to the individual study SDTM and ADAM datasets, and finally to the integrated summary of efficacy datasets. An audit of 10 percent of the raw data, including tumor measurements, laboratory values, age, and treatment discontinuation date, were compared and found to be consistent. These data tables were then used to prepare analyses that corroborated the analyses submitted by the applicant in the integrated summary of efficacy and summary of clinical efficacy.

Reviewer Comment:
The potential for the introduction of bias into objective response and PFS determination as per investigator (INV) in this single-arm trial was mitigated by incorporation of independent radiologic review (IRR) of trial imaging studies, which generally supported the investigator analysis. Given the challenges of precision in CT evaluation of ovarian cancer, there were some discrepancies between INV and IRR that underwent further scrutiny during the FDA analysis, but which did not reveal overt systematic bias on the part of the investigator. The study part with the greatest difference was the subject of a BIMO investigation initiated by the Applicant. Indeed, the inter-operator variability between the two IRR evaluators was meaningful, underscoring the challenges of imaging in this disease setting.

Patient Disposition

Of the 106 patients in the efficacy population, 37 (34.9%) had responses ongoing at the time of data lock. Of the patients who had discontinued treatment, 48 (69.6%) had discontinued due to disease progression. Two additional patients (2.9%) were discontinued from study therapy due to increases in CA-125 from baseline, though this was not a prospectively-defined criterion for disease progression and drug discontinuation. These latter two cases are captured as protocol deviations in Study 10, above. Additional details of patient disposition for the efficacy population are provided in Table 11, below.

Table 11 Disposition of Patients in the Rucaparib Efficacy Population

	N = 106 n (%)
End of Treatment Status	
Ongoing	37 (34.9)
Discontinued	69 (65.1)
Primary Reason for Discontinuation of Study Drug	
Progressive Disease	48 (69.6)
Clinical Progression	4 (5.8)
Adverse Event	9 (13.0)
Death	0
Withdrawal by Patient	4 (5.8)
Physician Decision	2 (2.9)
Other*	2 (2.9)
Lost to Follow-Up	0
Pregnancy	0
Protocol Deviation	0

Source: ISE ADSL.xpt
*Other includes two patients removed from study treatment due to increase in CA-125 blood level.

Demographics

Demographic characteristics

The clinical trials that provided data for this efficacy analysis enrolled patients from 50 sites in seven countries. While a large fraction of patients (24.5%) were from the U.S., patients were enrolled in six other countries, making up 75.5% of the efficacy population. Demographic details are presented in Table 12.

Table 12 Demographic Characteristics of the Rucaparib Efficacy Population

	N = 106
Age (years)	
Mean (SD)	59.2 (10.8)
Median	59.0
Min, Max	33.0, 84.0
Age Group n (%)	
< 50	28 (26.4)
51-60	30 (28.3)
61-70	34 (32.1)
71-80	11 (10.4)
81-90	3 (2.8)
Gender, F n (%)	106 (100)
Race n (%)	
Asian	7 (6.6)
Black	4 (3.8)
White	83 (78.3)
Other	2 (1.9)
Missing	10 (9.4)
Country n (%)	
U.S.	26 (24.5)
Australia	4 (3.8)
Canada	31 (29.3)
France	10 (9.4)
Great Britain	11 (10.4)
Israel	14 (13.2)
Spain	10 (9.4)
Baseline smoking status n (%)	
Current	6 (5.7)
Former	30 (28.3)
Never	70 (66.0)

Source: ISE ADSL.xpt

Reviewer Comment:
The generalizability of this population to the global population of women suffering from ovarian cancer is limited, as this population reflects the characteristics similar to a U.S. population. The age distribution of patients in the primary efficacy population appears somewhat younger than women diagnosed with ovarian cancer in the U.S., where the median age at diagnosis is 63 years. However, peak incidence occurs in the 55-64 year age group in the U.S., which is similar for the enrolled population.

Baseline Disease Characteristics

Baseline disease characteristics are summarized in Table 13. Platinum-sensitive is defined as: progression-free after the end of last platinum-based treatment regimen for at least 6 months.

Platinum-resistant is defined as: progression after the end of last platinum-based treatment regimen within 6 months. Platinum-refractory is defined as: progression during platinum therapy.

Table 13 Baseline Disease Characteristics in the Rucaparib Efficacy Population

	N = 106
ECOG	n (%)
0	65 (61.3)
1	41 (38.7)
BRCA mutation germline v somatic*	
gBRCAm	88 (83.0)
sBRCAm	18 (17.0)
Mutated BRCA Locus	
BRCA1	67 (63.2)
BRCA2	39 (36.8)
Tumor histology	
Epithelial ovarian cancer	
Endometroid	3 (2.8)
Mixed	4 (3.8)
Other	1 (0.9)
Serous	83 (78.3)
Fallopian tube cancer	
Mixed	1 (0.9)
Serous	8 (7.6)
Primary peritoneal cancer	
Serous	6 (5.7)
Time since diagnosis, months	
>6-12	2 (1.9)
>12-24	3 (2.8)
>24	101 (95.3)
Mean	60.1
Median	51.7 (6.3-196.6)
Platinum Responsive Status	
Platinum-Sensitive	79 (74.5%)
Platinum-Resistant	20 (19%)
Platinum-Refractory	7 (6.5%)

Source: ISE ADSL.xpt
**Somatic BRCA mutation was defined as CTA or CDx deleterious BRCA mutation with normal germline analysis by local testing.*

Reviewer Comment:
All women included in the efficacy population had ECOG performance status of 0 or 1, suggesting that this population may be healthier than the general ovarian cancer population in the U.S. This is reflected by entry criteria that excluded women suffering from disease-specific complications, such as bowel obstruction. The assessment of germline versus somatic BRCAm performed by the sponsor is an exploratory analysis based on a comparison of the results of germline testing (either the NGS BROCA

assay performed at [redacted] (b) (4) *or other local laboratory-developed test [LDT]) with the results of the tumor tissue-based Foundation Medicine, Inc., NGS clinical trial assay. This assay and the related companion diagnostic device did not directly adjudicate detected BRCA mutations as originating from germline or somatic mutations. Instead, when the tumor tissue result was consistent with BRCA mutation and the germline result was wildtype, the tumor status was coded by the applicant as containing a somatic mutation. All other BRCAm was considered genomic mutation. Of the 106 patients in the primary efficacy population, 18 were determined to have tumors with somatic mutations based on this algorithm.*

The distribution of histologic variants of Mullerian duct tumors represented in this trial appears to be similar to that of the general population.

A large number of patients on the study, 101 (95.3%) were at least 24 months from their primary diagnosis, which reflects the platinum-sensitive nature of BRCAm tumors.

Table 14 describes prior treatment regimens and interval since last therapy.

Table 14 Prior Treatment Regimens in the Primary Rucaparib Efficacy Population

	N = 106
Number of prior platinum regimens	n (%)
2	60 (56.6)
3	40 (37.7)
>3	6 (5.7)
Platinum-free interval (months)	
<6	27 (25.5)
>6-12	56 (52.8)
>12-24	18 (17.0)
>24	5 (4.7)
Number of prior regimens	
2	41 (38.7)
3	43 (40.6)
4	20 (18.9)
>5	2 (1.9)

Source: ISE ADSL.xpt

Reviewer Comment:
Eighty percent of the efficacy population prior treatment with 2-3 platinum-containing regimens, consistent with the protocol; patients with a variety of platinum-free intervals are represented. Some patients had prior treatment with non-platinum regimens, as well.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The investigator or designee was responsible for distributing the appropriate strength(s) of rucaparib tablets to patients, with a sufficient number of tablets provided to each patient to last until the next scheduled visit. Patients recorded daily doses of rucaparib using a trial-specific patient diary provided by the sponsor or designee, in which trial site personnel entered the scheduled daily doses and the number of tablets to be taken. Patients were to bring their remaining rucaparib and diary to the next scheduled visit. Trial site personnel reviewed the dosing information with the patient (or legally authorized representative) on scheduled clinic visit days and performed a compliance check and tablet count. Patients meeting noncompliance criteria were required to discontinue trial treatment. Trial site personnel recorded compliance information on the eCRF and retained the patient diary in the patient's medical record.

Efficacy Results

Table 15 presents the best overall response as evaluated by the investigator and the IRR. The ORR as per the investigator was 54% (95%CI: 44%, 64%) and per the IRR was 42% (95%CI: 32%,52%).

Table 15 Best Objective Response in the Rucaparib Efficacy Population as per the Investigator and IRR

Response	INV N=106 n(%)	IRR N=106 n(%)
ORR CR+PR [95% CI]	57 (54) [44,64]	44 (42) [32,52]
CR	9	5
PR	48	39
PD	9	17
SD	24	40
NE	4	5
Ongoing with a single response	1	
Ongoing without a response	11	

Source: ISE ADOR dataset.

There were 57 patients with an objective response as assessed by the investigator, and 44 patients according to the IRR. There were 41 patients who were considered responders by both the investigator and IRR, 16 patients were considered responders only by investigator while three patients were responders only by IRR. Of the 16 patients who were considered to be responders only by investigator, 11 were classified as SD, two as NE and three as PD. Of the three patients who were considered to be responders by IRR two were classified as SD and one as ongoing without a response by investigator. The

distribution of the best overall response by investigator and IRR is presented in Table 16. Discrepancy between investigator assessment and IRR varied by trial section, with 7% in Study 10 part 2B, 25% in ARIEL2 part 1, and 10% in ARIEL2 part 2. In ARIEL2 part 1, 11 of 24 patients had discordant best overall response assessment. This included 5 patients with a PR by investigator and SD by IRR, 3 patients with a CR by investigator and a PR by IRR, 1 patient with a PR by investigator and a CR by IRR, 1 patient with a PR by investigator and PD as by IRR, and 1 patient with SD by investigator and PD by IRR. These 11 scans were subjected to independent review by the sponsor, and seven of these were found to be without error, including two patients scored by investigator as having achieved PR but not by IRR. In the remaining 4 patients the independent peer reviewer found 3 errors by the investigator, including lesion selection at screening, assessment of non-target lesion progression, or determination of date of progression, and 1 error by IRR, which was lack of identification of target at screening.

Table 16 Distribution of the Best Overall Response (BOR) as per Investigator and IRR in the overall efficacy population (N=106).

	BOR as per IRR					
BOR as per INV	**CR**	**NE**	**PD**	**PR**	**SD**	**Total**
CR	2	1	0	4	2	9
NE	0	3	1	0	0	4
PD	0	0	8	0	1	9
PR	3	1	3	32	9	48
SD	0	0	4	2	18	24
Ongoing with a single response	0	0	0	0	1	1
Ongoing without a response	0	0	1	1	9	11
Total	5	5	17	39	40	106

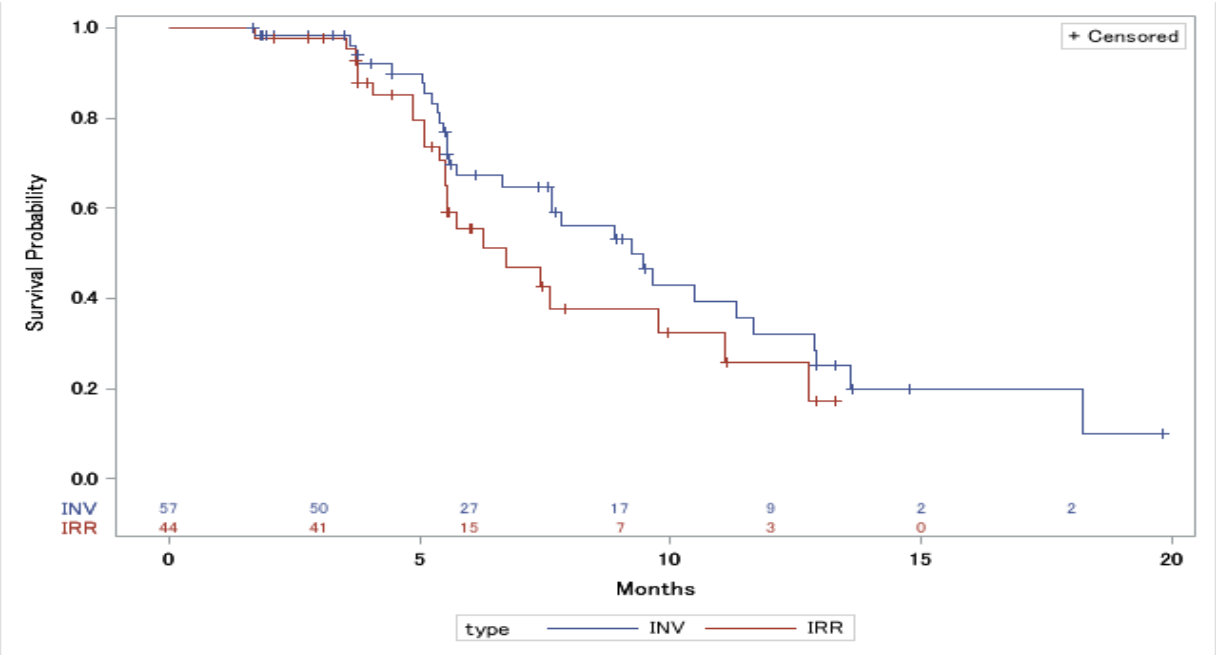
Source: ISE ADOR dataset.
Reviewer Comment:
Taken as a whole, the investigator and IRR discrepancies do not strongly influence the benefit-risk assessment or the estimation of the antitumor response seen with rucaparib. It is recognized that in general, and in open-label studies in particular, investigators report higher response rates than independent reviewers.

Durability of Response

Figure 2 displays the Kaplan-Meier curves for duration of response by the investigator in blue and as per IRR in red for patients having an objective response. Table 17 summarizes the median duration of response and the distribution of patients having a durable response in three month categories. The DOR as per investigator was 9.2 months and 6.7 months as per IRR. The percentage of patients losing a

response to PD was the same in both the investigator and IRR assessments. About 30% of the patients had a response that lasted for about 6 months.

Figure 2: KM Curves of the DOR for the Patients with Objective Response as per the Investigator and IRR.



Source: ISE ADEF dataset.

Table 17 Duration of Response in Patients with Objective Response as per the Investigator and IRR.

	INV (N=57) n (%)	**IRR (N=44) n (%)**
Median DOR in months (95% CI)	**9.2 (6.6,11.7)**	**6.7 (5.5,11)**
Events (PD)	30 (53)	23 (52)
<=3 months	13 (22.8)	12 (27.3)
3-6 months	17 (29.8)	17 (38.6)
6-9 months	9 (15.8)	8 (18.2)
9-12 months	9 (15.8)	4 (9.1)
>1 year	9 (15.8)	3 (6.8)

Source: ISE ADEF dataset.
Reviewer Comment:
The duration of response for rucaparib treatment appears similar to durations of response with other third-line treatment approaches in platinum-sensitive ovarian cancer, though few prospective trials are available to evaluate treatment effects in this setting, particularly in the BRCAm subgroup. The approved PARP inhibitor olaparib, used in fourth-line treatment of gBRCAm ovarian cancer, demonstrated a 7.9 month duration of response in an open-label, single-arm trial in a group of patients likely to be somewhat more chemoresistant.

Additional Analyses Conducted on the Trials

Subpopulations

Table 18 summarizes the ORR and DOR as assessed by the investigator for different subgroups of interest. For patients having a response, the distribution of the DOR in six-month categories is also presented. A majority of the patients seem to sustain their response for about 6 months.

Table 18 ORR and median DOR as per the investigator assessments summarized by various categories.

Variable	ORR n (%) (95% CI)	Median DOR (95% CI)	DOR <= 6months n/N (%)	DOR 6-12 months n/N (%)	DOR >1 year n/N (%)
Mutation Type*					
Germline (n=88)	47 (53.4) (42.5, 64.1)	9.5 (7.6, 12.9)	23/47 (48.9)	16/47 (34)	8/47 (17)
Somatic (n=18)	10 (55.6) (30.8, 78.5)	5.5 (1.7, NR)	7/10 (70)	2/10 (20)	1/10 (10)
Age					
<65 (n=68)	35 (51.5) (39, 63.8)	8.9 (5.5, 11.7)	19/35(54.3)	11/35(31.4)	5/35(14.3)
>=65 (n=38)	22 (57.9) (40.8, 73.7)	9.7 (6.6, NR)	11/22(50)	7/22(31.8)	4/22(18.2)
Race					
Non-white (n=13)	6 (46.2) (19.2, 74.9)	7.6 (4.4, NR)	3/6(50)	2/6(33.3)	1/6(16.7)
Unknown (n=10)	5 (50) (18.7, 81.3)	NR (9.2, NR)	3/5(60)	1/5(20)	1/5(20)

Variable	ORR n (%) (95% CI)	Median DOR (95% CI)	DOR <= 6months n/N (%)	DOR 6-12 months n/N (%)	DOR >1 year n/N (%)
White (n=83)	46 (55.4) (44.1, 66.3)	9.7 (5.7, 12.9)	24/46 (52.2)	15/46 (32.6)	7/46 (15.2)
BRCAm by Companion Diagnostic Device, FoundationFocus BRCACDx™					
NA (n=6)	5 (83.3) (35.9, 99.6)	NR (1.7, NR)	4/5 (80)	0	1/5 (20)
Negative (n=4)	1 (25) (0.6, 80.6)	3.8 (NE, NE)	1/1 (100)	0	0
Positive (n=49)	27 (55.1) (40.2, 69.3)	11.7 (7.6, 18.2)	12/27 (44.4)	9/27 (33.3)	6/27 (22.2)
BRACA1/2					
BRCA1 (n=67)	36 (53.7) (41.1, 66)	9.7 (7.6, 12.9)	15/36 (41.7)	14/36 (38.9)	7/36 (19.4)
BRCA2 (n=39)	21 (53.8) (37.2, 69.9)	7.6 (5.5, 12.9)	15/21 (71.4)	4/21 (19)	2/21 (9.5)
Number of Prior Chemotherapy Regimens					
2 (n=41)	28 (68.3) (51.9, 81.9)	7.8 (5.7, 12.9)	12/28 (42.9)	11/28 (39.3)	5/28 (17.9)
>2 (n=65)	29 (44.6) (32.3, 57.5)	11.3 (5.6, 12.9)	18/29 (62.1)	7/29 (24.1)	4/29 (13.8)
Number of Prior Platinum-Based Chemotherapy Regimens					
2 (n=60)	39 (65) (51.6, 76.9)	8.9 (5.7, 12.9)	19/39 (48.7)	14/39 (35.9)	6/39 (15.4)
>2 (n=46)	18 (39.1) (25.1, 54.6)	11.3 (5.5, 13.6)	11/18 (61.1)	4/18 (22.2)	3/18 (16.7)
Platinum-Free Interval					
<6 (n=27)	5 (18.5) (6.3, 38.1)	NR (3.8, NR)	5/5 (100)		

Variable	ORR n (%) (95% CI)	Median DOR (95% CI)	DOR <= 6months n/N (%)	DOR 6-12 months n/N (%)	DOR >1 year n/N (%)
>=6-12 (n=56)	35 (62.5) (48.5, 75.1)	8.9 (5.5, 11.3)	21/35 (60)	10/35 (28.6)	4/35 (11.4)
>12-24 (n=18)	14 (77.8) (52.4, 93.6)	9.7 (6.6, NR)	4/14 (28.6)	7/14 (50)	3/14 (21.4)
>24 (n=5)	3 (60) (14.7, 94.7)	13.6 (9.2, NR)		1/3 (33.3)	2/3 (66.7)
Platinum Sensitivity					
Refractory (n=7)	0 (0, 41.0)				
Resistant (n=20)	5 (25) (8.7, 49.1)	NR (3.8, NR)	5/5 (100)		
Sensitive (n=79)	52 (65.8) (54.3, 76.1)	9.5 (6.6, 11.7)	25/52 (48.1)	18/52 (34.6)	9/52 (17.3)
ECOG Performance Status					
0 (n=65)	37 (56.9) (44, 69.2)	9.5 (7.6, 11.7)	17/37 (45.9)	13/37 (35.1)	7/37 (18.9)
1 (n=41)	20 (48.8) (32.9, 64.9)	9.2 (4.4, NR)	13/20 (65)	5/20 (25)	2/20 (10)
Geographical Region					
US (n=26)	17 (65.4) (44.3, 82.8)	11.7 (5.6, 18.2)	9/17 (52.9)	5/17 (29.4)	3/17 (17.6)
non-US (n=80)	40 (50) (38.6, 61.4)	8.9 (5.6, 11.3)	21/40 (52.5)	13/40 (32.5)	6/40 (15)

Source: ISE ADEF,ADOR datasets; NE-not estimable NR-not reached

Reviewer Comment:
Some of these exploratory subgroup analyses, such as the BRCA mutant status by companion diagnostic and platinum free interval, had a limited number of patients. In addition, these analyses are exploratory with no multiplicity adjustment and no pre-specified hypotheses. In the few patients that had platinum

refractory or resistant ovarian cancer, the observed ORR appears to be low. No other outlier subgroup was observed.

11.3.2. Integrated Assessment of Effectiveness

The data submitted by the applicant for the efficacy evaluation include all patients with advanced ovarian cancer, with deleterious tBRCAm, and who received at least two prior chemotherapy treatment regimens and were treated on one of two clinical trials with rucaparib 600 mg BID. These patients were treated on clinical trials that were exploring the MTD of rucaparib (Study 10) and evaluating the susceptibility of tumors with homologous recombination repair-deficient (HRD) states to rucpaparib as defined by an assay that is still in development (ARIEL2). The original development plan for this agent was based in part on identification of non-BRCAm subsets of ovarian cancer patients who would potentially receive benefit from rucaparib treatment based on the hypothesis that defects in multiple homologous repair pathway genes could cause cells to be susceptible to PARP inhibition. At the time of the most recent discussion with the applicant regarding rucaparib efficacy and HRD score, response rates for the non-BRCAm cohort were low.

For the purposes of this application, and after agreement between the applicant and FDA, an efficacy population was defined by appropriate selection criteria. This population—patients with BRCAm ovarian cancer and at least two prior platinum-based treatment regimens with platinum-sensitive relapse—is a patient population with a life-threatening condition and an unmet medical need for new safe and effective treatment options. The intention was to evaluate the efficacy of rucaparib in this population using a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval. Objective responses to treatment are an indication of anti-tumor activity. When the rate of objective response is an improvement over available therapy, and when those responses are durable, the prediction of benefit of treatment with rucaparib can be supported in this patient population.

Few controlled studies are available to benchmark response rates to traditional chemotherapy in the third-line platinum-sensitive setting. No trials are available that evaluates this endpoint, or any endpoint, for a BRCAm population, who, epidemiologically, appear to be more chemosensitive and have longer durations of response and survival. Traditional chemotherapy studies strictly follow convention regarding ovarian cancer as platinum sensitive or resistant, and therefore, comparison of the group as a whole is difficult. Standard treatment for third-line, platinum-sensitive ovarian cancer (a cohort included in the CALYPSO trial, Pujade-Laurraine, JCO 2010) was later reported as 39% - 45% for platinum-sensitive patients who were progression free for 6-12 months after platinum, to 38% - 42% for patients with platinum-free intervals of >24m, the latter of whom are thought to be more chemosensitive. Given these rates, compared with the platinum-sensitive population in this application of 68%, this appears to be a meaningful improvement in a surrogate endpoint. For platinum-resistant disease, response rates on the AURELIA study (which included only patients who had been treated with two or fewer prior lines of therapy) were 28% (95% CI: 21-36) in the chemotherapy plus bevacizumab group (and higher in the un-prespecified bevacizumab plus paclitaxel subgroup at 53%). However the rucaparib treated platinum-resistant subgroup, which demonstrated an ORR of 25%, was a more refractory line of therapy, as all

patients were treated with rucaparib in the fourth or fifth line treatment setting where responses would be expected to be less. Therefore, extrapolation to other studies is not possible. In addition, in the AURELIA study, no information was available on the frequency of BRCA mutations and no outcome data is available in this particular subset.

In the analysis of the primary efficacy population submitted in this application, women with BRCAm ovarian cancer had a meaningful 54% ORR to rucaparib treatment and this rate is supported by response durations of 9.2 months, an alteration of disease natural history in this setting. For this patient population, this translates into an effective treatment period while avoiding the repeated and cumulative toxicity of a platinum-based regimen, the current standard of care. Patients defined conventionally as platinum-resistant and platinum-refractory experienced lower rates of response and duration. However, these patients have even fewer treatment options that demonstrate efficacy.

To mitigate risk associated with accelerated approval based on a surrogate endpoint reasonably likely to predict clinical benefit, there are two ongoing clinical trials to confirm benefit. The first trial, ARIEL3, evaluates rucaparib monotherapy versus placebo as maintenance in the BRCA-mutation positive platinum-sensitive relapse setting. If positive, this study will establish rucaparib efficacy in an earlier line of therapy than the current indication, confirming clinical benefit and supporting regular approval. This trial is fully accrued, and preliminary results are expected in Q1 2018. The second trial, ARIEL4, is a planned multicenter, open-label, randomized trial of rucaparib versus chemotherapy in patients with BRCA-mutated relapsed ovarian cancer, which, if positive, will establish the superiority of single-agent rucaparib over traditional third-line chemotherapy. This trial is planned to open to accrual in late 2016, with interim results expected in late 2022.

The label should concisely describe the populations in which rucaparib was assessed for this application, without detailed descriptions of the individual trials, since the populations are treated similarly and aggregated for the review. Efficacy should be described in the label using the primary analysis, the investigator-assessed ORR, with summary statements regarding DOR and the supportive IRR analysis. Additionally, summary data should be presented for the platinum-sensitive population as well as the resistant/refractory population, as these represent meaningful clinical differences in both patient prognosis and treatment efficacy.

11.4. Review of Safety

11.4.1 Safety Review Approach

The safety of rucaparib was evaluated in three studies in which patients with advanced ovarian cancer or other solid tumors received 600 mg po BID of rucaparib. The studies include (refer to Table 4 for additional details):

1. Study CO-338-010, a phase 1/2 single arm, open label study in patients with advanced gBRCA mutant ovarian cancer and solid tumors,

2. ARIEL 2, a phase 2 single arm, open label study in patients with relapsed ovarian cancer; and

3. Study CO-338-023 (RUCAPANC), a phase 2 single arm open label study in patients with previously treated locally advanced or metastatic pancreatic cancer and a deleterious BRCA mutation.

The applicant's primary safety analyses included 409 patients; 378 with ovarian cancer and, of those, 144 with BRCA mutated ovarian cancer treated with at least one dose of 600mg of rucaparib. This reviewer's primary safety analyses, except for the analyses of death, were based on data from the 378 patients with ovarian cancer, as this represents the most closely related population to the indication. The safety analysis population for the analyses of death included the total 409 patients that received rucaparib 600 mg BID. The patients with "other tumors" were from the phase 1/2 study CO-338-010 and the phase 2 study CO-338-023 in patients with pancreatic cancer. Of note, one of the 378 patients who was categorized as an ovarian cancer patient was later found not to have ovarian cancer, but endometrial cancer (data submitted at the time of the safety update). Therefore, this patient was removed from labeling, but is included in our analyses below.

Data for Phase 3 Study CO-338-014 (ARIEL 3), which is a blinded study evaluating rucaparib versus placebo as maintenance therapy, (b) (4) as the study is blinded and ongoing. (b) (4)

Reviewer Comment:
As noted above, at the time of the 60-day update, one of the patients included in the safety analyses of ovarian cancer patients, patient CO-338-010-013302, was found to actually have had endometrial cancer. The patient was placed in the "other types of tumors" group and 60-day update analyses were completed with the adjusted numbers. The reclassification does not significantly change the analysis.

11.4.2. Review of the Safety Database

Overall Exposure

The safety population supporting this application arises from three clinical studies, CO-338-010, ARIEL2, and CO-338-023 as described above. Exposure was assessed with the ovarian cancer patients only, both mBRCA and non-BRCA mutated. Rucaparib exposure was adequate to assess safety with 28.8% of all ovarian cancer patients and 43.1% of mBRCA ovarian patients receiving treatment between 6 months to 12 months, and 14.3% of all ovarian cancer patients and 19.4% of mBRCA ovarian patients receiving treatment past 12 months. The median relative dose intensity was 0.91 in the all ovarian cancer group compared with 0.85 in the mBRCA ovarian group. Table 19 Safety Population by Study and Subgroup describes the safety population.

Table 19 Safety Population by Study and Subgroup

	mBRCA Ovarian Cancer (N=144)	Non-BRCA Ovarian Cancer (N=234)	All Other Tumor Types (N=31)	Total (N=409)
600 mg				
Phase 1				
Study CO-338-010				
Part 1	5	0	2	7
Phase 2				
Study CO-338-010				
Part 2	42	0	0	42
Part 3	16[a]	0	10[a]	26
Study ARIEL2				
Part 1	41	163	0	204
Part 2	40	71	0	111
Study CO-338-023	0	0	19	19
Total	**144**	**234**	**31**	**409**

Source: SCS

[a] *A patient with a diagnosis of endometrial cancer was incorrectly included in the ovarian category instead of the "other tumor type" category. This was corrected in the 60 day safety update.*

Reviewer comment: Overall, the size of the safety population and the extent of exposure were adequate and generally allowed sufficient characterization of AEs associated with rucaparib in the target population.

Relevant characteristics of the safety population:

In the ovarian cancer patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range: 6 -197). The demographics and baseline characteristics of the safety population are shown in Table 20.

Table 20 Summary of Demographics

	mBRCA Ovarian Cancer (N=144)	All Ovarian Cancer (N=378)
Age		

Median, years	59	62
Range, years	33 - 84	31 - 86
≤60	81 (56.2)	167 (44.2)
>60 and ≤70	44 (30.6)	135 (35.7)
>70	19 (13.2)	76 (20.1)
Countries		
United States	41 (28.5)	143 (37.8)
Non-US North America	35 (24.3)	83 (22.0)
Europe	49 (34.0)	120 (31.7)
Other	19 (13.2)	32 (8.5)
Race, n (%)		
White	116 (80.6)	303 (80.2)
Asian	10 (6.9)	22 (5.8)
Black or African American	4 (2.8)	8 (2.1)
Other	4 (2.8)	7 (1.9)
Missing	10 (6.9)	38 (10.1)
ECOG Performance Status at Baseline, n(%)		
0	85 (59.0)	233 (61.6)
1	59 (41.0)	145 (38.4)
Time Since Cancer Diagnosis (months)		
Median	45.9	42.7
Range	6.3 - 196.6	6.3 - 196.6

Source: SCS Table 2.7.4-8

Adequacy of the safety database:

The size of the safety database and duration of rucaparib exposure were sufficient to characterize the safety of rucaparib for treatment of a serious and life-threatening condition, with the expectation of updated safety data from ARIEL2 and from the ongoing randomized phase III trial, ARIEL3. ARIEL3 will evaluate rucaparib compared with placebo in the maintenance setting in a similar patient population to that of ARIEL2.

Demographics and disease characteristics of the study subjects were adequately representative of the target population of patients with ovarian cancer who have been treated with prior platinum-containing chemotherapy.

11.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission contained all required components of eCTD and was well organized, allowing for a substantive review of all contents. Adverse events (AEs) from a subset of case report forms for studies CO-338-010, ARIEL2, and CO-338-023 were reviewed and compared to the datasets in order to confirm accuracy of the data transfer. Overall, there did not appear to be any significant discrepancies between the case report forms that were audited and the datasets in the NDA. Verbatim terms for a subset of Grade 3, 4, and 5 (NCI CTCAE v 4.03) AEs were compared to the corresponding MedDRA lower level terms and AE coding was deemed adequate.

The overall quality and integrity of the application appear reasonable.

Categorization of Adverse Events

The applicant's safety analyses were based on the safety population, which was defined as all patients who initiated treatment with rucaparib at 600 mg BID in Studies CO-338-010, ARIEL2, and CO-338-023 and received at least 1 dose of rucaparib as of the data cut-off dates (n=409). Safety data tables were presented for the following groups: mutant BRCA ovarian cancer, non-BRCA ovarian cancer, all ovarian cancer, other tumor types, and the total safety population.

Adverse events (AEs) were monitored from the time that informed consent was obtained until 28 days after the last dose of rucaparib

Treatment-emergent adverse events (TEAEs) were defined as AEs with onset dates on or after the date of first dose of rucaparib through the date of the last rucaparib dose plus 28 days.

The applicant presented the analyses of safety both for overall incidence of adverse events occurring during the study, i.e., treatment emergent adverse events (TEAEs) and as treatment related TEAEs. The latter categorization was based on the applicant/investigators assessment of an adverse event's relatedness to rucaparib.

Reviewer comment: This reviewer's safety analysis was based on the overall incidence of TEAEs regardless of the applicant's decision on causality, given that the supporting studies were single arm open label studies.

Verbatim AE terms were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 18.1. The severities of the AEs and laboratory abnormalities were graded according to the NCI CTCAE grading system (Version 4.03). For AEs not covered by NCI CTCAE, the severity was characterized as mild, moderate, severe, or life-threatening.

Certain similar MedDRA Preferred Terms (PTs) were combined and presented as overall frequencies for the combined terms, as well for the individual PT within the appropriate SOC. The combined terms and the individual terms were:

• ALT/AST increased: ALT increased, AST increased;

• Anemia and/or low/decreased hemoglobin: anemia, hemoglobin decreased;
• Asthenia/fatigue: asthenia, fatigue;
• Neutropenia and/or low/decreased ANC: neutropenia, neutrophil count decreased;
• Thrombocytopenia and/or low/decreased platelets: platelet count decreased, thrombocytopenia.

Reviewer comment:
In addition to the applicant's combined terms, this reviewer identified the following terms for combination in the analyses of SAEs by preferred term and the TEAEs by preferred term tables. Abdominal pain (abdominal pain, abdominal pain upper and abdominal pain lower), and intestinal obstruction (intestinal obstruction, small intestinal obstruction and large intestinal obstruction) were combined so as not to underestimate the incidence of these AEs.

Definitions for serious adverse events (SAEs) and the reporting of the SAEs were based on the International Conference on Harmonisation [ICH] guidance document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Based on specific adverse events previously observed across drugs in the same class (PARP inhibitors), and these events observed during the rucaparib development program, the applicant determined that some adverse reactions were of particular interest in the evaluation of safety. These adverse events, termed adverse events of special interest (AESI), include myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Routine Clinical Tests

The routine clinical testing of patients enrolled in the clinical trials, including efforts to examine adverse event data by monitoring laboratory tests and vital signs, appear to have been adequate. Recommendations for increased monitoring of cbcs in the incidence of prolonged anemia were made (mandated) in light of the development of the AESIs myelodysplastic syndrome and acute myeloid leukemia identified following prolonged anemia and myelosuppression.

11.4.4. Safety Results

Deaths

There were 60 deaths (15%) in the overall safety population of 409 patients that received 600mg BID of Rucaparib. A higher proportion of patients with "other" tumors died (45%, 14/31 patients) compared to patients with ovarian cancer (12%, 46/378 patients). The majority (52/60, 87%) of deaths were due to progressive disease. TEAEs with an outcome of death were reported in 14 out of 409 (3.4%) patients, including 5 patients (5/144, 3.5%) with BRCA mutant ovarian cancer. The frequency of TEAEs resulting in death was higher in patients with other tumors (n = 5, 16.1%) compared to those with ovarian cancer (n

= 9, 2.4%). The most frequently-reported TEAE resulting in death was malignant neoplasm progression (10 patients, 2.4%). See Table 21 for a summary of TEAEs resulting in Death.

Table 21 TEAEs Resulting in Death in the Overall Safety Population (Combined Studies CO-338-010, ARIEL2, and CO-338-023)

600 mg BID					
TEAE	**Ovarian Cancer mBRCA N=144**	**Ovarian Cancer Non-BRCA N=234**	**All Ovarian Cancer N=378**	**Other Tumors N=32**	**Overall N=409**
			n(%)		
Total Deaths	14 (9.7)	32 (14)	46 (12)	14 (45)	60 (15)
Any AE occurring within 28 days of therapy (TEAE) with an outcome of death	5 (3.5)	4 (1.7)	9 (2.4)	5 (16)	14 (3.4)
Malignant Neoplasm Progression	5 (3.5)	3 (1.3)	8 (2.1)	2 (6.5)	10 (2.4)
Upper Gastrointestinal Hemorrhage	0	0	0	1 (3.2)	1 (0.2)
Dyspnea	0	0	0	1 (3.2)	1 (0.2)
Pulmonary Embolism	0	0	0	1 (3.2)	1 (0.2)
Sepsis	0	1 (0.4)	1 (0.3)	0	1 (0.2)
Hyponatremia	1 (0.7)	0	1 (0.3)	0	1 (0.2)
Acute Kidney Injury	0	0	0	1 (3.2)	1 (0.2)

Source: ADAE.xpt, Narratives, SCS Table 2.7.4-16

Within the overall safety population, 12 patients died due to a TEAE during the treatment period, defined as being within 28 days of the last dose of rucaparib, as of the clinical visit cut-off date of April 29, 2016.

Three of these 12 patients died for reasons other than disease progression. All three were non-ovarian cancer patients: one with small cell carcinoma of the throat, one with pancreatic cancer, and one with colon cancer. The primary reason for death for the three patients of other tumor types included pulmonary embolism and pneumonia, dyspnea and one patient with acute kidney injury and upper GI hemorrhage. Table 22 summarizes the narratives for the patients who died within 28 days of rucaparib therapy for reasons other than progression of disease.

Table 22: Narratives for Patients in the Overall Safety Population Who Died Within 28 Days of Treatment from Causes Other Than Disease Progression

Patient ID Group	Tumor Type	Summary of Case	Reviewer Comment
CO-338-010-013315	Other mBRCA	78 year old male with metastatic small cell carcinoma of the throat associated with BRCA2 mutation and a history of shortness of breath. Concomitant medications included megesterol acetate, dexamethasone and fluticasone/salmeterol. He received his first dose of rucaparib (b) (6), followed by his second and last dose (b) (6) during the food-effect portion of the study. He was hospitalized on (b) (6), after presenting with shortness of breath. The patient was diagnosed with a pulmonary embolism and rucaparib was held. He became progressively more short of breath and died on (b) (6), 17 days after the last dose of rucaparib. Repeat CT chest imaging was consistent with progressive disease, stable pulmonary embolism and new bilateral infiltrates consistent with possible pneumonia.	While it is possible that the death could be attributed to the documented pulmonary embolism, review of the medical records is more consistent with stable pulmonary embolism at the time of death. The cause of death is likely multifactorial with new onset pneumonia, possible disease progression, and underlying pulmonary embolism.
CO-338-010-043312	Other mBRCA	71 year old female with metastatic colon cancer associated with a gBRCA2 mutation and metastases to the lung and liver. Past medical history included resection of pulmonary metastases. The patient received her first dose of rucaparib (b) (6). Thirty-eight days after initiating rucaparib, the patient was hospitalized with worsening dyspnea, productive cough, an oxygen saturation of 90% and bibasilar crackles. Study treatment was held. CT imaging revealed extensive bilateral pulmonary infiltrates, multiple lung nodules, small bilateral pleural effusions, and ruled out a pulmonary embolism. The patient's symptoms did not significantly improve with BiPAP, antibiotics, methylprednisolone to address possible hypersensitivity reaction, and atypical infection. She was transferred to	While the pulmonary symptoms could possibly be related to inflammatory causes such as pneumonitis, there was also evidence of disease progression within the lungs. Available records indicate the patient did not appear to respond to steroid therapy. Though there are documented metastases to the lung, there is not enough information to rule out pneumonitis.

		hospice and died on (b) (6), 23 days since her last dose of study drug. The cause of death on the death certificate was listed as underlying colon cancer, and the SAE was subsequently changed to respiratory failure as a result of a follow up SAE report.	
CO-338-023-32035-107	Other mBRCA	41 year old male diagnosed (b) (6) with metastatic pancreatic cancer associated with BRCA2 mutation. Past medical history included deep vein thrombosis and pulmonary embolism. Concomitant medications included enoxaparin sodium. The patient initiated rucaparib on December 26, 2014. On (b) (6), he underwent paracentesis, removing 5 liters of malignant ascites. He was hospitalized (b) (6), for abdominal pain and ascites. Paracentesis was again performed. Creatinine was 2.0, uric acid> 7 and potassium 6.7. The patient underwent dialysis for acute kidney injury. INR was 5.9 secondary to coagulopathy felt due to hepatic metastases. An endotracheal tube revealed hematemesis, the patient went into cardiac arrest and died on (b) (6) The AKI was felt to have been secondary to large fluid shifts complicated by concomitant NSAID use. Upper GI hemorrhage was felt due to coagulopathy secondary to malignancy.	While it is possible due to timing the acute kidney failure could be related to rucaparib, it is more likely to be related to the fluid shifts resulting from large volume paracentesis. It is unlikely that the upper GI hemorrhage is related to rucaparib and more likely due to a coagulopathy secondary to hepatic metastases.

Source: Narratives, CRFs

Reviewer Comment:
The majority of the deaths were from disease progression. Though the investigator classified three patients as having died from causes other than progressive disease, the ability to definitively define cause of death in these cases is limited to available records. After review of the narratives and CRFs, the cause of death is multifactorial with disease progression likely contributing in patients CO-338-010-013315 and CO-338-010-043312.

The remaining 9 patients who died due to an adverse event within 28 days of treatment, died from progressive disease, and are summarized in Table 23.

Table 23 Narratives for Patients Who Died Within 28 Days of Treatment from Disease Progression

Patient ID Group	Tumor Type	Summary of Case	Reviewer Comment
CO-338-010-042242	Ovarian Cancer mBRCA	75 year old female with advanced primary peritoneal cancer involving the large and small intestine associated with a gBRCA2 mutation. The patient initiated treatment (b) (6). Three days after initiating therapy, the patient was hospitalized for Grade 2 small bowel obstruction. Rucaparib was held until symptoms resolved in 8 days. Treatment restarted (b) (6). Treatment was again held (b) (6), for Grade 3 elevated ALT and AST, and resumed when levels improved (b) (6). Rucaparib was permanently discontinued (b) (6), when the patient was hospitalized for recurrent bowel obstruction secondary to disease progression. The patient entered hospice care and died on (b) (6), due to disease progression.	The patient had known metastatic disease to the bowel upon initiating therapy. It is likely the primary cause of death is SBO secondary to disease progression and not related to rucaparib.
CO-338-010-092220	Ovarian Cancer mBRCA	66 year old female with metastatic fallopian tube cancer associated with a gBRCA1 mutation. Metastatic disease included diffuse peritoneal carcinomatosis. Past medical history included bilateral breast cancer curatively treated and COPD. Concomitant medications included rivaroxaban and nebulized arformoterol. The patient initiated treatment on (b) (6). Rucaparib dose was held for vomiting (b) (6), and dose reduced for Grade 3 fatigue (b) (6). She was hospitalized for acute abdominal pain (b) (6), likely secondary to constipation. A CT scan of the abdomen revealed intrahepatic biliary ductal dilation as well as increased enhancement and loculation involving the peritoneum. Her symptoms improved and rucaparib was restarted. On (b) (6), the patient was found to have a hemoglobin of 4.8 g/dL	It is likely the primary cause of death is accurate and not related to the ongoing SAE of anemia or to rucaparib treatment.

		and was transfused a total of 6 units of PRBCs. Rucaparib was held. She was hospitalized for colonoscopy and EGD which was unrevealing. The rucaparib was restarted at a reduced dose of 240 mg BID on (b) (6). The anemia was assessed as related to study therapy. The patient was hospitalized (b) (6), after being diagnosed with progression of disease and rucaparib was discontinued. The patient died on (b) (6) due to malignant neoplasm progression.	
CO-338-010-602204	Ovarian Cancer mBRCA	52 year old female with metastatic ovarian cancer associated with a gBRCA1 mutation. Past medical history included lymphedema and hydronephrosis with nephrostomy tube placement. Rucaparib was initiated on (b) (6) The patient was hospitalized (b) (6) and underwent thoracentesis for left pleural effusion that was negative for malignant cells. She was re-hospitalized (b) (6), for dyspnea. On (b) (6), the patient was found to be hyponatremic with sodium 129 mmol/L and had recurrent hyponatremia despite treatment. She was diagnosed with clinical progression of disease with new umbilical metastases, and elected for palliative care only. Rucaparib was discontinued (b) (6), and the patient died (b) (6). Death was due to malignant neoplasm progression and hyponatremia.	While the ongoing hyponatremia may have contributed to the cause of death, it is likely the primary cause is accurate as progression of disease.
CO-338-017-31006-203	Ovarian Cancer	54 year old female with metastatic high grade serous primary peritoneal cancer not associated with a BRCA mutation. Rucaparib was initiated (b) (6) The patient was hospitalized (b) (6) due to bowel obstruction felt secondary to her underlying cancer. The patient remained hospitalized with abdominal pain, distension, and nausea and vomiting. She died on (b) (6) The cause of death assessed as bowel obstruction	The reviewer agrees with the attribution of death as progression of disease that is not likely related to rucaparib**.**

		from progression of cancer.	
CO-338-017-32018-202	Ovarian Cancer	77 year old female with metastatic ovarian cancer not associated with a BRCA mutation. The patient initiated rucaparib on (b) (6) Her total bilirubin was 41 on (b) (6), and the rucaparib was held. She was admitted to the hospital (b) (6), with nausea, vomiting, jaundice, and a bilirubin of 121. Ultrasound of the abdomen revealed a new 2.0 cm pancreatic mass with biliary ductal dilatation. Biliary drains were placed, bilirubin decreased to 3.3, and the patient was discharged (b) (6) She discontinued from the study due to disease progression (b) (6) and died (b) (6)	Given progression of disease noted 12 days prior to death, the cause of death is unlikely related to rucaparib. The reviewer agrees with the attribution of death as progression of disease.
CO-338-023-32032-101	Other mBRCA	45 year old male with stage 3 pancreatic adenocarcinoma associated with a BRCA1 mutation. He initiated rucaparib on (b) (6) Treatment was held due to Grade 3 increased ALT and AST on (b) (6). On (b) (6) he was hospitalized and treated for catheter related grade 3 sepsis and discharged. A reduced dose of rucaparib 480mg BID was initiated (b) (6) for elevated LFTs. Patient was noted to have disease progression on CT scans and rucaparib was discontinued (b) (6) The patient was admitted to hospice and died (b) (6)	Though the patient experienced initial grade 3 elevation of AST/ALT requiring dose reduction, the labs improved and were not likely related to cause of death. The patient had evidence of disease progression which was more likely cause of death**.**
CO-338-023-32032-104	Other mBRCA	62 year old male with metastatic pancreatic adenocarcinoma associated with a gBRCA2 mutation. Rucaparib was initiated (b) (6) Four days later, he was hospitalized with Grade 3 hepatic encephalopathy and rucaparib was held. Abdominal ultrasound showed multiple liver lesions and patient was discontinued from study due to progression of disease. The patient was discharged to hospice and died due to disease progression (b) (6)	The death is unlikely related to rucaparib given the likely progression of pancreatic cancer.

CO-338-023-32034-101	Other mBRCA	64 year old female diagnosed with stage 4 pancreatic adenocarcinoma associated with a gBRCA2 mutation. Past medical history included ovarian/peritoneal carcinoma June 2008. She received her first dose of rucaparib [redacted], and discontinued treatment the following day due to investigator decision. She had a Grade 3 pulmonary embolism prior to study entry on [redacted] which remained ongoing. The patient died on [redacted], due to malignant neoplasm progression of pancreatic cancer assessed as not related to rucaparib therapy.	The patient received a single dose of study drug. The death is unlikely related to rucaparib and more likely related to disease progression.
CO-338-023-32035-103	Other mBRCA	52 year old female diagnosed [redacted] with stage 4 pancreatic cancer associated with a gBRCA1 mutation. The patient initiated treatment with rucaparib (600 mg BID) on [redacted] On [redacted] the patient was hospitalized with Grade 3 nausea and vomiting, rucaparib was held, and a CT scan revealed gastric outlet obstruction secondary to increased pancreatic head mass. A duodenal stent was placed and the patient was discharged on [redacted] On [redacted], the patient developed Grade 3 anemia, Grade 4 increased bilirubin of 12.0 mg/dL and Grade 4 thrombocytopenia of 12 K/µL. Rucaparib was held and a CT scan of the abdomen/pelvis showed moderate intrahepatic duct dilation. Urine and blood cultures were positive for *Escherichia coli*. A percutaneous biliary drain was placed, her symptoms improved, and she was discharged on [redacted]. The patient withdrew from the study on [redacted], due to enrollment in hospice care. She died [redacted] The investigator reported her death as related to “disease under study.”	The patient had evidence of disease progression within the pancreatic head and was enrolled in hospice prior to her death. It is likely that the primary cause of death is accurate and not related to an ongoing SAE.

Source: Narratives, CRFs

Of the remaining 48 patients who died during the follow up period, the majority (43/48 patients) died due to progression of disease. Five patients died during the follow up period from unknown causes or causes not related to disease progression. Patient 17-16005-202 died of sepsis 72 days after her last dose of rucaparib. Patient 17-11004-202 died of 42 days after last dose due to “adverse event;” however, no adverse event information was provided and the patient discontinued rucaparib treatment due to clinical disease progression. Two patients (17-32005-207 and 17-32005-214) were missing causes of death and died 375 and 128 days after the last dose of rucaparib.

(b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

it is concerning that a signal for a causative relationship between rucaparib therapy and the eventual development of MDS or AML is present. This relationship has also been noted in olaparib, a drug of the same class, which to this date has had 26 cases of MDS/AML out of 5006 patients treated. All patients who received rucaparib, as well as the patients receiving olaparib, had received multiple chemotherapy regimens prior to receiving the study drug.

Serious Adverse Events

SAEs, regardless of causality, were experienced by 106 (28.0%) patients in the group of all ovarian cancer patients, with intestinal obstruction (6.1%), malignant neoplasm progression (5.0%), and anemia (4.8%) reported most frequently. In ovarian cancer patients with a BRCA mutation, intestinal obstruction (7.6%), malignant neoplasm progression (7.6%), and anemia (5.6%) continued to be the most frequently reported SAEs. The remaining SAEs, in both groups, occurred in ≤ 2.1% of patients. The SAEs are listed in Table 24.

Table 24 Serious Adverse Events by Preferred Term Experienced In ≥ 1% of Ovarian Cancer Patients

SOC PT	**Ovarian Cancer mBRCA N=144**	**All Ovarian Cancer N=378**
	n(%)	
Patient with any SAE	46 (32)	106 (28)
Gastrointestinal disorders		
Intestinal obstruction[a]	11 (7.6)	23 (6.1)
Abdominal pain[b]	2 (1.4)	5 (1.3)
Ascites	2 (1.4)	4 (1.1)
Vomiting	1 (0.7)	4 (1.1)
Nausea	1 (0.7)	4 (1.1)
Neoplasms benign, malignant and unspecified		
Malignant neoplasm progression	11 (7.6)	19 (5.0)
Blood and lymphatic system disorders		
Anemia	8 (5.6)	18 (4.8)
Febrile Neutropenia	1 (0.7)	4 (1.1)
Renal and urinary disorders		
Acute kidney injury	3 (2.1)	7 (1.9)
Infections and infestations		
Sepsis	2 (1.4)	6 (1.6)
Urinary tract infection	2 (1.4)	5 (1.3)

Pneumonia	2 (1.4)	4 (1.1)
Metabolism and nutrition disorders		
Dehydration	2 (1.4)	4 (1.1)
Respiratory, thoracic, and mediastinal disorders		
Pleural effusion	0	3 (0.8)

Source: ADAE.xpt, ISS Table 3.1.4

[a] *Includes intestinal obstruction, large intestinal obstruction and small intestinal obstruction*

[b] *Includes abdominal pain and abdominal pain upper*

Reviewer comment:

Though not combined in the applicant's submission, the reviewer combined the preferred terms intestinal obstruction, small intestinal obstruction and large intestinal obstruction, resulting in intestinal obstruction being the most frequent SAE. It is not uncommon for intestinal obstruction to develop in patients with metastatic ovarian cancer and review of the narratives revealed the majority of the patients had disease progression as the cause of the intestinal obstruction and was not a result of drug effects. Overall, when examining the SAEs in the all ovarian cancer group compared to the BRCA mutated ovarian cancer group, the numbers are similar, with a slightly higher percentage of the most common SAEs in the BRCA mutated group.

Dropouts and/or Discontinuations Due to Adverse Effects

TEAEs that led to treatment discontinuation, regardless of causality, occurred in 17% of all ovarian cancer patients. TEAEs leading to treatment discontinuation most frequently were malignant neoplasm progression (3.4%) followed by fatigue (2.1%) and intestinal obstruction (2.1%). Median times to discontinuation due to TEAE were similar for patients with BRCA-mutant ovarian cancer and patients with non-BRCA ovarian cancer (65 and 56 days, respectively). TEAEs leading to discontinuation in >1% of ovarian cancer patients is summarized in Table 25.

Table 25 TEAEs that Led to Discontinuation by Preferred Term in >1% in the Ovarian Cancer Population

SOC PT	**Ovarian Cancer mBRCA N=144**	**All Ovarian Cancer N=378**
	n(%)	
Any TEAE Leading to Discontinuation	24 (16.7)	64 (16.9)
Malignant Neoplasm Progression	8 (5.6)	13 (3.4)
Fatigue/Asthenia	1 (0.7)	9 (2.4)
Intestinal Obstruction[a]	3 (2.1)	8 (2.1)
Nausea	3 (2.1)	5 (1.3)
Abdominal Pain[b]	0	4 (1.1)

Source: ADAE.xpt, Table 2.7.4-20 SCS, Table 3.1.12.1.1 ISS

[a] *Includes intestinal obstruction and small intestinal obstruction*

[b] *Includes abdominal pain and abdominal pain upper*

Six additional patients discontinued treatment due to a TEAE between the initial NDA data cut-off on February 29, 2016, and the 60 day safety update data cut-off on April 29, 2016. Overall, 18.6% of patients discontinued treatment due to a TEAE in the safety update compared with 17.1% at the cut-off for the initial NDA. Malignant neoplasm progression remained the most frequently reported term (3.4%, 4.4% update), followed by fatigue and intestinal obstruction (2.1%, 2.4% update for both).

Reviewer comment:
There were no notable differences among the different safety populations. The majority of patients in both the subset of BRCA mutated ovarian cancer patients and the overall ovarian cancer populations experienced disease progression as the most frequent TEAE leading to discontinuation. The safety update does not change the interpretation of discontinuations. The dose modification guidelines implemented in the protocol appear appropriate due to a lower level of discontinuations from any one AE.

During the labeling review, the applicant identified additional patients, who, although discontinued due to Preferred Terms other than disease progression, actually discontinued due to disease progression. The applicant provided the following table, Table 26, listing these patients. This reviewer examined these cases and agreed that the patients all discontinued with disease progression. Therefore, these patients were not counted toward Adverse Reactions resulting in discontinuation in the label and the resulting percent of discontinuations due to ARs other than progression was changed from (b) (4) *to 10%.*

Table 26 Patients who discontinued rucaparib due to AE from disease progression not coded as disease progression

Patient Number	Adverse Event(s) by Preferred Term leading to Discontinuation	Date of Last Exposure	Progression Date
042243	Intestinal obstruction	21JUN2015	06JUL15*
043307	Ascites; Urinary tract infection	26NOV2015	08DEC15
202226	Metastases to central nervous system; Brain oedema	01JUN2015	03JUL2015
202240	Small intestinal obstruction	29JUL2015	29JUL2015
313322	Small intestinal obstruction	07OCT2015	NR (Patient discontinued due to the small intestinal obstruction)
602204	Malignant neoplasm progression; Dyspnoea	(b) (6)	
14001-505	Intestinal obstruction	07MAR2016	NR (patient discontinued due to the intestinal obstruction)
14002-501	Ascites	28MAR2016	29MAR2016
14008-205	Small intestinal obstruction	06MAY2015	08MAY2015
32004-201	Ascites	16JUN2015	15JUN2015
32008-201	Ascites; Abdominal Pain	27DEC2013	NR (Patient withdrew consent due to concerns about increasing ascites)
32012-201	Small intestinal obstruction	19SEP2014	19SEP2014*
32013-206	Small intestinal obstruction	03JUN2014	NR (Patient was discontinued due to the small intestinal obstruction)
32013-501	Obstruction gastric	08APR2016	30NOV2015
32016-201	Small intestinal obstruction	11JAN2015	12JAN2015
32021-203	Small intestinal obstruction; Sepsis; Intestinal perforation	27OCT2014	20OCT2014

NR=not reported

*Clinical progression per the Investigator. CT scan not done.

Source: Information Request dated 10.27.2016

Dose Reduction or Interruption

In ovarian cancer patients, 63.8% experienced a TEAE leading to dose reduction or interruption; 45.0% of patients experienced a TEAE leading to dose reduction and 56.9% of patients experienced a TEAE leading to treatment interruption. The most frequent TEAEs (≥ 5% of patients) that led to dose reduction or treatment interruption in ovarian cancer patients were combined terms of anemia/hemoglobin decreased (21.2%), combined terms of asthenia/fatigue (19.8%), nausea (17.2%), vomiting (11.4%), ALT increased (9.8%), combined thrombocytopenia/platelets decreased (9.8%), AST increased (6.6%) and terms of combined neutropenia/ANC decreased (6.3%).

In ovarian cancer patients with a BRCA mutation, 68.8% experienced a TEAE leading to dose reduction or interruption; 48.6% of patients experienced a TEAE leading to dose reduction and 56.9% of patients experienced a TEAE leading to treatment interruption. The most frequent TEAEs (≥ 5% of patients) that led to dose reduction or treatment interruption in ovarian cancer patients were combined terms of anemia/hemoglobin decreased (27.1%), combined terms of asthenia/fatigue (22.2%), nausea (16.7%), combined terms of thrombocytopenia/platelets decreased (11.8%), vomiting (11.1%), ALT increased (10.4%), and combined terms of neutropenia/ANC decreased (8.3%).

The median time to a TEAE that led to dose reduction or treatment interruption of rucaparib was comparable between patients with BRCA mutant ovarian cancer and all ovarian cancer patients (27 and 24 days, respectively).

TEAEs leading to dose reduction or interruption in ≥ 5% of ovarian cancer patients is summarized in Table 27. TEAEs leading to dose reduction alone are summarized in Table 28.

Table 27 TEAEs that Led to Dose Reduction or Interruption in ≥ 5% in the Ovarian Cancer Population

TEAE	Ovarian Cancer mBRCA N=144	All Ovarian Cancer N=378
	n (%)	
Any TEAE Leading to Dose Reduction or Interruption	**99 (68.8)**	**241 (63.8)**
Anemia[a]	39 (27.1)	80 (21.2)
Fatigue/ Asthenia	32 (22.2)	75 (19.8)
Nausea	24 (16.7)	65 (17.2)
Vomiting	16 (11.1)	43 (11.4)
Alanine aminotransferase Increased	15 (10.4)	37 (9.8)
Thrombocytopenia[b]	17 (11.8)	37 (9.8)
Aspartate aminotransferase Increased	11 (7.6)	25 (6.6)
Neutrophil count decreased[c]	12 (8.3)	24 (6.3)
Blood creatinine increased, AKI, renal impairment	7 (4.9)	19 (5.0)
Abdominal Pain[d]	9 (6.2)	18 (4.7)

Source: ADAE.xpt, Table 2.7.4-22 SCS, Table 3.1.15.1.1 ISS

[a] Includes anemia and hemoglobin decreased

[b] Includes thrombocytopenia and platelet count decreased

[c] Includes neutrophil count decreased and neutropenia

[d] Includes abdominal pain and abdominal pain upper

Table 28 TEAEs that Led to Dose Reduction in ≥ 5% in the Ovarian Cancer Population

Preferred Term	Ovarian Cancer mBRCA N=144		All Ovarian Cancer N=378	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
Any TEAE	**70 (48)**	**42 (30)**	**171 (45)**	**100 (26)**
Anemia[a]	33 (23)	23 (16)	63 (17)	48 (13)

Fatigue/Asthenia	23 (16)	6 (4)	50 (13)	12 (3)
Nausea	15 (10)	2 (1)	42 (11)	10 (3)
Thrombocytopenia[b]	7(5)	2(1)	17 (5)	5 (1)
Vomiting	5 (3)	1 (1)	20 (5)	4 (1)

Source: ADAE.xpt
[a] Includes anemia and hemoglobin decreased
[b] Includes thrombocytopenia and platelet count decreased

Reviewer Comment:
The most frequent adverse event leading to dose reductions or interruptions was anemia/decreased hemoglobin. Despite the higher numbers of dose modification, there were no discontinuations due to anemia, likely reflecting appropriate dosing modification guidelines. Though not identified by the applicant, the combined TEAEs of blood creatinine increased, AKI, and renal impairment led to dose reductions or interruptions in 5% of ovarian cancer patients.

Significant Adverse Events

Adverse events of interest are described in section 11.4.5 Analysis of Submission-Specific Safety Issues. Specifically, the adverse events of interest include; MDS/Leukemia, QT prolongation, anemia, and hepatic events. Grade 3 -5 Adverse Events occurring up to 28-days after last dose of study therapy, with frequency greater than or equal to 2%, are described in Table 30 below in the Treatment Emergent Adverse Events and Adverse Reactions section.

Treatment Emergent Adverse Events and Adverse Reactions

In the ovarian cancer safety population, treatment emergent adverse events (TEAEs) were experienced in 100% of patients and 100% of patients with BRCA mutated ovarian cancer. TEAEs occurring by MedDRA System Organ Classes (SOCs) up to 28-days after treatment discontinuation are shown in Table 29.

Table 29 Summary of System Organ Class Treatment Emergent Adverse Events

System Organ Class	**Ovarian Cancer mBRCA N=144**	**All Ovarian Cancer N=378**
	n (%)	
Gastrointestinal disorders	139 (96.5)	359 (95.0)
General disorders and administration site conditions	123 (85.4)	314 (83.1)
Nervous system disorders	98 (68.1)	242 (64.0)
Investigations	96 (66.7)	231 (61.1)
Metabolism and nutrition disorders	81 (56.3)	202 (53.4)
Blood and lymphatic system disorders	79 (54.9)	177 (46.8)
Infections and infestations	75 (52.1)	159 (42.1)

Respiratory, thoracic and mediastinal disorders	66 (45.8)	151 (39.9)
Skin and subcutaneous tissue disorders	64 (44.4)	149 (39.4)
Musculoskeletal and connective tissue disorders	58 (40.3)	140 (37.0)
Psychiatric disorders	32 (22.2)	82 (21.7)
Renal and urinary disorders	28 (19.4)	72 (19.0)
Vascular disorders	22 (15.3)	66 (17.5)
Injury, poisoning and procedural complications	28 (19.4)	50 (13.2)
Reproductive system and breast disorders	17 (11.8)	44 (11.6)
Eye disorders	18 (12.5)	37 (9.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (9.7)	28 (7.4)
Ear and labyrinth disorders	9 (6.3)	19 (5.0)
Cardiac disorders	9 (6.3)	18 (4.8)
Hepatobiliary disorders	3 (2.1)	7 (1.9)
Immune system disorders	3 (2.1)	7 (1.9)
Congenital, familial and genetic disorders	0	1 (0.3)
Endocrine disorders	1 (0.7)	1 (0.3)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Treatment emergent adverse events (TEAEs) occurred in all patients in the safety population of ovarian cancer patients. Table 30 lists TEAEs by preferred term occurring in ≥ 10% of patients occurring up to 28-days past treatment.

Table 30 Treatment Emergent Adverse Events by Preferred Term and Toxicity Grade ≥ 10% or > 2% Grade 3-5

	Ovarian Cancer mBRCA N=144			All Ovarian Cancer N=378		
System Organ Class Adverse Event	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
Gastrointestinal Disorders						
Nausea	110 (76.3)	6 (4.2)	0	290 (76.7)	18 (4.8)	0
Vomiting	72 (50.0)	8 (5.6)	0	173 (45.8)	15 (4.0)	0
Abdominal pain[a]	65 (45.1)	6 (4.2)	0	156 (41.3)	15 (4.0)	0
Constipation	56 (38.9)	1 (0.7)	0	146 (38.6)	5 (1.3)	0
Diarrhea	49 (34.0)	3 (2.1)	0	128 (33.9)	9 (2.4)	0
Abdominal distension	30 (20.8)	0	0	70 (18.5)	0	0
Stomatitis	17 (11.8)	0	0	35 (9.7)	1 (0.3)	0
Intestinal obstruction[b]	13 (9.0)	8 (5.6)	0	25 (6.6)	19 (5.0)	0
Ascites	7 (4.9)	2 (1.4)	0	20 (5.3)	9 (2.4)	0
General Disorders And Administration Site Conditions						
Fatigue	88 (61.1)	13 (9.0)	0	233 (61.6)	28 (7.4)	0
Asthenia	34 (23.6)	9 (6.3)	0	72 (19.1)	17 (4.5)	0
Edema Peripheral	16 (11.1)	1 (0.7)	0	41 (10.9)	1 (0.3)	0
Pyrexia	17 (11.8)	0	0	40 (10.6)	1 (0.3)	0
Blood And Lymphatic System Disorders						
Anemia[c]	75 (52.1)	40 (27.8)	0	161 (42.6)	88 (23.3)	0
Thrombocytopenia[d]	37 (25.7)	5 (3.5)	0	78 (20.6)	17 (4.5)	0
Neutropenia[e]	29 (20.1)	13 (9.0)	0	58 (15.3)	31 (8.2)	0
White blood cell count decreased	16 (11.1)	3 (2.1)	0	24 (6.4)	3 (0.8)	0
Nervous System Disorders						
Dysgeusia	55 (38.2)	0	0	147 (38.9)	0	0
Headache	36 (25.0)	1 (0.7)	0	69 (18.2)	1 (0.3)	0
Dizziness	26 (18.1)	2 (1.4)	0	62 (16.4)	2 (0.5)	0
Syncope	4 (2.8)	4 (2.8)	0	7 (1.8)	7 (1.8)	0
Investigations						
Alanine aminotransferase increased	64 (44.4)	17 (11.8)	0	145 (38.4)	38 (10.1)	0
Aspartate aminotransferase increased	62 (43.1)	4 (2.8)	0	136 (36.0)	14 (3.7)	0
Blood creatinine increased	33 (22.9)	0	0	75 (19.8)	2 (0.5)	0
Blood alkaline phosphatase increased	20 (13.9)	2 (1.4)	0	39 (10.3)	4 (1.1)	0
Hypomagnesemia	18 (12.5)	0	0	30 (7.9)	1 (0.3)	0
Hypokalemia	9 (6.3)	3 (2.1)	0	23 (6.1)	8 (2.1)	0
Hyponatremia	9 (6.3)	5 (3.5)	0	17 (4.5)	10 (2.7)	0

Hypophosphatemia	4 (2.8)	1 (0.7)	0	11 (2.9)	8 (2.1)	0
Metabolism And Nutrition Disorders						
Decreased Appetite	49 (34.0)	3 (2.1)	0	188 (38.1)	11 (2.9)	0
Respiratory, Thoracic And Mediastinal Disorders						
Dyspnea	28 (19.4)	1 (0.7)	0	80 (21.1)	2 (0.5)	0
Cough	27 (18.8)	1 (0.7)	0	55 (14.6)	1 (0.3)	0
Infections and Infestations						
Urinary tract infection	26 (18.1)	4 (2.8)	0	54 (14.3)	8 (2.1)	0
Upper respiratory tract infection	23 (16.0)	0	0	39 (10.3)	0	0
Sepsis	2 (1.4)	2 (1.4)	0	6 (1.6)	6 (1.6)	1 (0.3)
Musculoskeletal And Connective Tissue Disorders						
Back Pain	17 (11.8)	2 (1.4)	0	41 (10.9)	3 (0.8)	0
Arthralgia	17 (11.8)	1 (0.7)	0	33 (8.7)	1 (0.3)	0
Pain in Extremity	17 (11.8)	0	0	29 (7.7)	1 (0.3)	0
Skin And Subcutaneous Tissue Disorders						
Photosensitivity reaction	12 (8.3)	0	0	38 (10.1)	0	0
Alopecia	19 (13.2)	0	0	34 (9.0)	0	0
Pruritus	19 (13.2)	0	0	32 (8.5)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Malignant neoplasm progression	11 (7.6)	6 (4.2)	5 (3.5%)	20 (5.3)	11 (2.9)	8 (2.1%)

Source: ADAE.xpt

[a] *Includes abdominal pain, abdominal pain upper and abdominal pain lower*

[b] *Includes intestinal obstruction, small intestinal obstruction and large intestinal obstruction*

[c] *Includes anemia, hemoglobin decreased, hematocrit decreased and RBC count decreased*

[d] *Includes thrombocytopenia and platelet count decreased*

[e] *Includes neutropenia and neutrophil count decreased*

The review of safety evaluated additional potential toxicities of study drug therapy through analyses of the incidence of AEs based on hierarchical composites of MedDRA preferred terms (i.e., high level terms) and a hierarchical composites of MedDRA high level terms (i.e., high level group terms) in each treatment group. The common high level terms in the ovarian cancer population are nausea and vomiting symptoms (82.0%), asthenic conditions (76.7%), liver function analyses (44.4%), anemias (41.8%) and gastrointestinal and abdominal pains (41.8%). Table 31 and Table 32 summarize the incidence of high level terms and high-level group terms respectively occurring in ≥ 10% occurring up to 28-days post treatment.

Table 31 Treatment Emergent Adverse Events (≥ 10%) by High Level Term

High Level Term	Ovarian Cancer mBRCA N=144 n (%)	All Ovarian Cancer N=378 n (%)
Nausea and vomiting symptoms	119 (82.6)	310 (82.0)
Asthenic conditions	112 (77.8)	290 (76.7)
Liver function analyses	73 (50.7)	168 (44.4)
Anemias NEC	74 (51.4)	158 (41.8)
Gastrointestinal and abdominal pains (excl oral and throat)	66 (45.8)	158 (41.8)
Gastrointestinal atonic and hypomotility disorders NEC	59 (41.0)	157 (41.5)
Sensory abnormalities NEC	56 (38.9)	149 (39.4)
Appetite disorders	50 (34.7)	146 (38.6)
Diarrhea (excl infective)	49 (34.0)	128 (33.9)
Breathing abnormalities	34 (23.6)	90 (23.8)
Flatulence, bloating and distension	34 (23.6)	81 (21.4)
Musculoskeletal and connective tissue pain and discomfort	36 (25.0)	81 (21.4)
Renal function analyses	35 (24.3)	77 (20.4)
Headaches NEC	38 (26.4)	72 (19.1)
Neurological signs and symptoms NEC	28 (19.4)	67 (17.7)
Upper respiratory tract infections	36 (25.0)	65 (17.2)
Coughing and associated symptoms	28 (19.4)	60 (15.9)
Urinary tract infections	26 (18.1)	56 (14.8)
Thrombocytopenias	22 (15.3)	48 (12.7)
Rashes, eruptions and exanthems NEC	19 (13.2)	44 (11.6)
Edema NEC	17 (11.8)	43 (11.4)
White blood cell analyses	22 (15.3)	41 (10.9)
Febrile disorders	17 (11.8)	40 (10.6)
Stomatitis and ulceration	19 (13.2)	39 (10.3)
Tissue enzyme analyses NEC	20 (13.9)	39 (10.3)
Bladder and urethral symptoms	14 (9.7)	38 (10.1)
Feelings and sensations NEC	17 (11.8)	38 (10.1)
Photosensitivity and photodermatosis conditions	12 (8.3)	38 (10.1)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Table 32 Treatment Emergent Adverse Events (≥ 10%) by High Level Group Term

High Level Group Term	Ovarian Cancer mBRCA N=144 n (%)	All Ovarian Cancer N=378 n (%)
Gastrointestinal signs and symptoms	131 (91.0)	339 (89.7)
General system disorders NEC	119 (82.6)	308 (81.5)
Gastrointestinal motility and defecation conditions	86 (59.7)	223 (59.0)
Neurological disorders NEC	79 (54.9)	206 (54.5)
Hepatobiliary investigations	73 (50.7)	168 (44.4)
Anemias nonhemolytic and marrow depression	74 (51.4)	158 (41.8)
Appetite and general nutritional disorders	50 (34.7)	146 (38.6)
Infections - pathogen unspecified	67 (46.5)	143 (37.8)
Respiratory disorders NEC	62 (43.1)	140 (37.0)
Epidermal and dermal conditions	49 (34.0)	118 (31.2)
Musculoskeletal and connective tissue disorders NEC	37 (25.7)	85 (22.5)
Renal and urinary tract investigations and urinalyses	35 (24.3)	78 (20.6)
Headaches	39 (27.1)	73 (19.3)
Hematology investigations (incl blood groups)	34 (23.6)	68 (18.0)
Electrolyte and fluid balance conditions	25 (17.4)	62 (16.4)
Urinary tract signs and symptoms	23 (16.0)	53 (14.0)
Skin appendage conditions	28 (19.4)	51 (13.5)
Muscle disorders	20 (13.9)	49 (13.0)
Platelet disorders	22 (15.3)	48 (12.7)
Oral soft tissue conditions	20 (13.9)	47 (12.4)
Bone, calcium, magnesium and phosphorus metabolism disorders	21 (14.6)	46 (12.2)
Sleep disorders and disturbances	18 (12.5)	46 (12.2)
Enzyme investigations NEC	21 (14.6)	42 (11.1)
Body temperature conditions	17 (11.8)	41 (10.9)
Joint disorders	20 (13.9)	39 (10.3)
White blood cell disorders	18 (12.5)	39 (10.3)
Physical examination and organ system status topics	15 (10.4)	33 (8.7)
Injuries NEC	20 (13.9)	32 (8.4)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Reviewer Comments:

1. *The common TEAEs reported in the ovarian cancer patients with a BRCA mutation were consistent with those observed within the overall ovarian cancer population.*
2. *For labeling purposes, the applicant updated the Adverse Reactions Tables to reflect the 60 day safety update data. In addition, at the time of the 60-day safety update, a patient initially counted in the safety population as ovarian was found to actually be an endometrial cancer patient. As a result of this pathology confirmation, adjustment of the all ovarian cancer patient population was changed from 378 to 377. Therefore, the numbers in labeling are slightly different from the numbers presented above, however, not in a meaningful way. The largest difference, which is only 2%, is with respect to the preferred term of Anemia, Grade 3-4. The*

percentage of patients treated with rucaparib experiencing anemia went from 23% to 25%. The reviewer agrees with these adjustments and also with the analyses performed generating labeling recommendations.

3. *The data submitted in the 60-day safety update does not change the interpretation of the safety signal in a meaningful way and was included in labeling.*

Laboratory Findings

Abnormalities in both hematologic and non-hematologic tests were primarily Grade 1 to 2 in severity. The most notable laboratory abnormality was hemoglobin, primarily decreased hemoglobin as reflected in the shift tables. This is consistent with the increased incidence of anemia as an adverse event. Grade 1-4 hemoglobin abnormalities were seen in 75.7% of all ovarian cancer patients and 78.5% of mBRCA ovarian patients. Anemia is discussed further in section 11.4.5. Analysis of Submission-Specific Safety Issues.

Grade 1-4 hematologic abnormalities (lymphocytes, hemoglobin, platelet count, and neutrophil count) occurred at similar rates overall in the mBRCA ovarian cancer group compared with the all ovarian cancer group, the majority being Grades 1-2. Grade 3-4 hematologic abnormalities occurred less frequently, in all groups except for decreased hemoglobin, which occurred in 21.4% of the all ovarian cancer patients and 25.7% of the mBRCA ovarian patients.

Grade 1-4 non-hematologic abnormalities (AST, ALT, Cholesterol, creatinine and glucose) were also similar in their overall incidence between the all ovarian and mBRCA ovarian cancer groups. The most frequent Grade 1-4 abnormality was creatinine at 97.1% and 95.8%, respectively. These were almost entirely Grade 1-2.

The majority of abnormalities in liver function tests were primarily Grade 1 to 2 in severity. The incidence of Grade 1-4 AST and ALT abnormalities were similar in both the mBRCA (77.1% and 75.7%) and overall ovarian groups (78% and 77.2%). Grade 3-4 abnormalities in ALT occurred at a higher rate than Grade 3-4 AST abnormalities in the all ovarian patients (13.5% vs 4.5%) as well as the mBRCA ovarian patients (15.3% vs 2.8%). Hepatic transaminitis is discussed further in section 11.4.5. Analysis of Submission-Specific Safety Issues.

Table 33 below summarizes Grade 1-4 laboratory abnormalities occurring in > 35% of patients while on rucaparib treatment or within 28 days of last dose of therapy.

Table 33 On-Treatment Laboratory Abnormalities > 35% in Patients Treated with 600 mg Rucaparib: Ovarian Cancer Population

Lab Parameter	Ovarian Cancer mBRCA N=144		All Ovarian Cancer N=378	
	Grade 1-4 n(%)	Grade 3-4 n(%)	Grade 1-4 n(%)	Grade 3-4 n(%)
Hematology				
Lymphocytes (absolute)	70 (48.6)	7 (4.9)	196 (51.9)	24 (6.3)
Hemoglobin	113 (78.5)	37 (25.7)	286 (75.7)	81 (21.4)
Platelet Count	67 (46.5)	7 (4.9)	157 (41.5)	22 (5.8)
Neutrophils	51 (35.4)	15 (10.4)	133 (35.2)	37 (9.8)
Renal Function				
Creatinine	138 (95.8)	0	367 (97.1)	4 (1.1)
Liver Function Tests				
Aspartate Aminotransferase (AST)	111 (77.1)	4 (2.8)	295 (78.0)	17 (4.5)
Alanine Aminotransferase (ALT)	109 (75.7)	22 (15.3)	292 (77.2)	51 (13.5)
Chemistries				
Glucose (Hyperglycemia)	86 (59.7)	6 (4.2)	214 (56.6)	15 (4.0)
Cholesterol	106 (73.6)	6 (4.2)	258 (68.3)	10 (2.6)

Source: SCS Table 2.7.4-25

Other laboratory data collected demonstrated similar laboratory parameters which worsened from baseline between both groups. See Table 34 for a summary of shifts in laboratory parameters from baseline while on treatment or within 28 days of last dose of therapy.

Table 34 Shifts in Laboratory Parameters in Patients Treated with Rucaparib: Ovarian Cancer Population

Laboratory Parameters	CTCAE Grade			
	600 mg BID			
	Ovarian Cancer mBRCA N=144		All Ovarian Cancer N=378	
	Grade 1-4 n(%)	Grade 3-4 n(%)	Grade 1-4 n(%)	Grade 3-4 n(%)
Decrease in hemoglobin	97 (67.4)	37 (25.7)	246 (65.1)	80 (21.2)
Decrease in lymphocytes	47 (32.6)	7 (4.9)	154 (40.7)	24 (6.3)
Decrease in platelets	61(42.4)	7 (4.9)	145 (38.4)	22 (5.8)
Decrease in neutrophils	50 (34.7)	15 (10.4)	129 (34.1)	37 (9.8)
Increase in creatinine	126 (87.5)	0	349 (92.3)	4(1.1)

Increase in AST	102 (70.8)	4 (2.8)	276 (73.0)	17 (4.5)
Increase in ALT	106 (73.6)	22 (15.3)	280 (74.1)	51 (13.5)
Increase in cholesterol	60 (41.7)	6 (4.2)	152 (40.2)	10 (2.6)

Source: SCS Table 2.7.4-25

Reviewer Comment:
The higher rate of Gr 3-4 events in decreased hemoglobin are consistent with anemia being the most frequent TEAE leading to dose reduction or treatment interruption in ovarian cancer patients. Increases in ALT or AST from baseline to a worsening CTCAE Grade occurred in 74.1% and 73.0% of patients, respectively, mainly to Grade 2 or less. The ALT/AST elevations tended to occur early in treatment and resolve or stabilize over time, consistent with only one discontinuation due to elevated transaminases.

Vital Signs

Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in systolic blood pressure, diastolic blood pressure, heart rate, or temperature were observed during the course of treatment.

Electrocardiograms (ECGs)

Central ECG monitoring was performed in Part 1 of Study CO-338-010. Triplicate 12-lead ECGs were taken at Screening, Day -8 and Day -7 prior to Cycle 1 (food-effect PK evaluation cohorts only), Day -1 prior to Cycle 1 (all patients), Days 1, 15, and 22 of Cycle 1 (all patients), Day 1 of Cycles 2 and beyond (all patients), and at the End-of Treatment Visit (all patients).

In Study CO-338-010 Part 2A, local ECGs were taken for all patients at screening, Day 1 of every cycle, at the End-of-Treatment Visit. In Study CO-338-010 Part 3, Study CO-338-017, and Study CO-338-023, local ECGs were taken at screening and at the End-of-Treatment Visit. A Cardiac Safety Report provided analyses of serial ECGs from Part 1 (Phase 1 portion) of the Study CO-338-010, which consisted of 10 dose-escalation cohorts of patients. ECG data from 56 patients was obtained with doses ranging from 40 mg QD to 840 mg BID. The primary endpoint for analyses was change from Baseline in QTcF. The results are discussed in the QT section, Section 11.4.5 Analysis of Submission-Specific Safety Issues, Arrhythmias/QTc Prolongation and the Interdisciplinary Review Team (IRT) for QT Studies Consultation.

QT

The Phase 1 (Part 1) dose-escalation portion of Study CO-338-010 included serial ECGs and independent central review in order to assess the effect of oral rucaparib on QTc. An independent lab performed the data analysis and generated a Cardiac Safety Report.

The primary endpoint for analysis of QTc was change from baseline in QTcF (ΔQTcF). A total of 55 patients were evaluable and ECG data were available for up to 22 cycles in the patient with the longest duration on treatment. In doses up to 840 mg BID, rucaparib administered daily, showed a trend for

prolongation of cardiac repolarization in proximity to time of administration, with increasing dose level, and with increasing concentration. At the 600 mg BID dose, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec. No patient within the study had a QTc >500 msec, but the FDA Interdisciplinary Review Team (IRT) for QT Studies Consultation concluded that the QTc appeared to prolong with increased doses, and a positive concentration-QTc relationship was observed. Please see section 11.4.5 Analysis of Submission-Specific Safety Issues, Arrhythmias/QTc Prolongation and the Interdisciplinary Review Team (IRT) for QT Studies Consultation: Thorough QT Study Review, for full discussion and analysis regarding QT prolongation.

Immunogenicity

Review of clinical safety does not raise concerns of immunogenicity with this small molecule. No formal immunogenicity studies were required or were done.

11.4.5. Analysis of Submission-Specific Safety Issues

Myelodysplastic Syndrome/Acute Myeloid Leukemia

In the overall safety population of 409 patients, there were 2 patients (0.49%) diagnosed with myelodysplastic syndrome (MDS) in the initial NDA submission. One patient with breast cancer from study CO-338-010 was BRCA mutated and one ovarian cancer patient from CO-338-017 was BRCA wild type.

(b) (4)

Within the 60 day safety update, one additional patient in the safety population, on Study CO-338-017, was reported as being diagnosed with AML between the initial NDA cut-off and the SCS Update cutoff date of April 29, 2016. The patient was an ovarian cancer patient with wild type BRCA. There were no additional MDS cases reported.

Cytogenetic abnormalities observed in the 3 cases of AML were primarily in chromosomes 5 and 7, consistent with those described in patients with MDS/AML secondary to previous cytotoxic chemotherapy. It is notable that most of the patients had received multiple prior cytotoxic regimens, including platinum, taxanes and additional alkylating agents. The duration of rucaparib treatment ranged from 57 to 427 days. In many cases, patients experienced a variable duration of cytopenias prior to diagnosis with MDS, often requiring delays and modifications of rucaparib dosing.

The applicant implemented study guidances requiring close monitoring of patients for hematological toxicity and evaluations as appropriate, including bone marrow biopsy, if toxicity did not resolve with treatment modification. The study drug was to be discontinued if MDS/AML was confirmed.

Overall, there have been a total of (b) (4) patients diagnosed with either MDS or AML, out of (b) (4) patients treated with oral rucaparib as described in Table 35.

Table 35 Patient Cases of Adverse Events of Myelodysplastic Syndromes or Acute Myeloid Leukemia

Study	Patient Number	Tx Arm	Age	Cancer Under Study	BRCA Mutation Status	Days On Study Drug Until Dx	Prior Chemotherapy Regimen(s) for Disease Under Study (# of cycles, if reported)	Prior Breast CancerDx/Tx	Dx	Cytogenetics	Outcome
(b) (4)											
CO-338-017 Part 2	16007-501	Rucaparib	68	Ovarian	BRCA wt	57	1 .Carboplatin + paclitaxel+ bevacizumab (6) 2. Carboplatin + pegylated liposomal doxorubicin (6) 3. Paclitaxel (6)	No prior breast cancer	RCMD MDS	ND	Discontinued rucaparib treatment

CO-338-010 Part 3	11-33-01	Rucaparib	57	Breast	gBRCA	155	1. Doxorubicin and cyclophosphamide followed by paclitaxel + anastrazole 2. Letrozole 3. Exemestane + Everolimu 4. Capecitane 5. Docetaxel + protein- bound paclitaxel + fulvestrant 6. Doxorubicin + exemestane Capecitabine	-----	IPPS-1 low risk MDS	ND	Patient remained on rucaparib as the patient had an ongoing PR. MDS was managed with supportive care (epoetin alfa, filgrastim, and transfusions).
CO-338-017 Part 2	31003-204	Rucaparib	8	Ovarian	$BRCA^{wt}$	539	1.Carboplatin+paclitaxel (6) 2. Epirubicin+cisplatin +capecitabine (6) 3. Carboplatin +doxorubicin(6)	No Prior Breast cancer	AML	Complex Karyotype with 2 abnormal clones. Abnormalities were found in chromosomes 5, 14, 15, 16, 17, 21 and X. FISH was positive for a 5q31 deletion and in 24% of cells.	Patient received weekly red blood cell transfusions to stabilize blood counts. The option of azacitidine therapy was discussed and the patient was to receive the treatment at her local hospital.

Source: Narratives and eCRFs, SCS Table 2.7.4-23, SCS 60-day Safety Update Table 2.7.4-19
AML = acute myeloid leukemia; BRCA = breast cancer gene; Dx = diagnosis; gBRCA = germline BRCA; IPPS = International Prognostic Scoring System; MDS = myelodysplastic syndrome; NA = not available; ND = not done; NSCLC = non-small cell lung cancer; PR = partial response; RCMD = refractory cytopenia with multilineage dysplasia; Tx = treatment

Arrhythmias/QTc Prolongation

In the safety population of 378 ovarian cancer patients, one patient experienced a Grade 4 arrhythmia of Torsade de Pointes. The patient, 16005-202, on study CO-338-017, had a Grade 4 SAE of Arrhythmia Secondary to Congenital QTC Syndrome on study day 22. The patient had had a history of previous episodes of prolonged QTc, and a provisional diagnosis of a congenital prolonged QT syndrome had been made. Results of genetic testing were pending at the time of this event. She initiated rucaparib at a dose of 600 mg BID 3 weeks prior, which had been held for one week due to dyspneic cough at the time of onset of the AE. The patient was hospitalized and treated with antiarrhythmics. The event of arrhythmia was considered resolved with sequelae and the patient was discharged from the hospital. Rucaparib was never re-started due to subsequent rehospitalization for sepsis. No QTC correction by the Fridericia's formula (QTcF) > 500 ms was reported for this patient, and the absolute increase in QTcF from baseline for this patient was unknown.

No other patient had a Grade 4 arrhythmia; one patient had a Grade 3 tachycardia CO-338-017-14002-202. Please see the Interdisciplinary Review Team (IRT) for QT Studies Consultation: Thorough QT Study Review, for full discussion and analysis regarding QT prolongation.

Reviewer Comment:
Although one patient had a serious event with a Grade 4 arrhythmia of Torsade de Pointes, it does not appear that rucaparib poses a significant risk of arrhythmia and therefore this is not included as a warnings and precautions. According to the IRT, the QTc appears to prolong with increased doses, and a positive concentration-QTc relationship was observed. The IRT review concluded that "at the median Cmax in ovarian cancer patients treated with Rubraca 600 mg twice daily, clinically relevant QTc prolongation exceeding 10 ms is expected." They proposed that the above language be included in the label under Pharmacodynamics; Cardiac Electrophysiology, in section 12.2. We did not feel that the QTc prolongation of ~10ms was clinically relevant so the "clinically relevant" language was not included in labeling.

Anemia

The reviewer included the following terms: anemia, hemoglobin decreased, hematocrit decreased and RBC count decreased as AEs representing Anemia. Anemia was one of the most common TEAE in all ovarian cancer patients (42.6%) and BRCA mutated ovarian cancer patients (52%) at all toxicity grades. It was the most frequent cause of Grade 3/4 TEAEs, occurring in 27.8% of all ovarian cancer patients and in 23.3% of BRCA mutated patients. There were no Grade 5 TEAEs in either group.

Anemia was managed with supportive care as well as with dose interruption and/or dose reduction(s). Anemia was the most common cause for dose reductions of rucaparib, in 63 (17%) of the all ovarian

cancer patients and 33 (23%) BRCA mutated ovarian cancer patients. Despite this, there were no discontinuations due to anemia.

A total of 35 patients in the total safety population (8.6%) received an anti-anemia concomitant medication (eg, iron preparation, erythropoietin) either as a supplement prior to initiating rucaparib (n=17; 4.2%) or as treatment for anemia while receiving rucaparib (n=17; 4.2%), with 1 patient (0.2%) taking iron supplements prior to initiating rucaparib and requiring epoetin beta during treatment with rucaparib. Among ovarian cancer patients, 109 (28.8%) received 1 or more (range = 1 to 10) blood transfusions during treatment with rucaparib. In ovarian cancer patients with a BRCA mutation, 48 (33.3%) received 1 or more (range = 1 to 9) blood transfusions during treatment with rucaparib. The median time to a blood transfusion was approximately 2 months in all ovarian cancer patients.

Reviewer Comment: Though anemia was one of the most common TEAEs occurring in the ovarian cancer population, and was the most frequent cause for dose reductions, it was well managed allowing patients to remain on study and did not result in any discontinuations.

Hepatic Transaminits and Drug Induced Liver Injury (DILI)

The following hepatic AEs were identified by the reviewer: hepatic pain, hepatomegaly, hyperbilirubinemia, jaundice, ALT increased, ammonia increased, AST increased, blood Alk Phos increased, blood Bilirubin increased, GGT increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased. This composite hepatic AE occurred in 175 patients (46.3%) in the ovarian cancer population and 77 patients (53.5%) in the BRCA mutated ovarian subgroup. The most frequent AEs (≥2%) in the ovarian cancer population were ALT increased, AST increased, blood Alk Phos increased, blood bilirubin increased and GGT increased. Of these hepatic events, 51 (13.5%) patients in the ovarian cancer population experienced a Grade 3 or 4 event. No patients had a Grade 5 event. Only 2 events were deemed to be serious and these are described below:

Patient CO-338-017-11006-203 with Grade 3 increased ALT had no history of transaminitis nor hepatic metastases. Rucaparib was initiated on (b) (6). On day 15 the AST was 85 U/L (normal 0-31), Grade 1, and ALT was 113 U/L(normal 0-34) , Grade 2. Bilirubin and alk phos were within normal range. On day 29, the ALT was increased to 235 U/L, Grade 3, and AST was 143 U/L, Grade 2. Rucaparib was held. By day 43, the Grade 3 ALT had resolved to Grade 1, 73 U/L. Grade 1 and 2 lab abnormalities were ongoing and rucaparib was then restarted at a reduced dose of 480 mg BID. Bilirubin and alk phos remained within normal range. The patient continued on study with no further dose interruptions or modifications due to hepatic events until discontinued for clinical disease progression (b) (6) day 321.

Patient CO-338-017-28001-203 with Grade 3 increased transaminases had a history of liver metastases and an intra-abdominal abscess one month prior to beginning rucaparib. Rucaparib was started (b) (6). On day 92 the patient was hospitalized with Grade 3 transaminitis, anemia, and asthenia. AST was 168 U/L (normal: 10-30), ALT 248 U/L (normal: 7-34), alkaline phosphatase 186 U/L (normal: 20-90), GGT 112 U/L (normal: 6-40), bilirubin 9.58 µmol/L (normal: 4.27-16.59). Rucaparib was held, and treatment

included dexamethasone, enoxaparin, insulin, lorazepam, and morphine. Labs on day 98 at discharge were AST 145 U/L, ALT 192 U/L, Alk phos 145 U/L, GGT 124 U/L, bilirubin 8.72 µmol/L. By day 110 the AST and ALT had normalized. Rucaparib was restarted at a dose of 480 mg BID on day 112. There were no further dose interruptions or modifications due to hepatic events until rucaparib was permanently discontinued day 121 for disease progression.

The rate of dose modifications (interruptions or reductions) for hepatic related AEs was similar between the BRCA mutated and overall ovarian cancer populations. ALT elevations resulted in dose modifications in 10.4% of the BRCA mutated and 9.8% of the overall ovarian population. AST elevations resulted in dose modifications in 7.6% of the BRCA mutated and 6.6% of the overall ovarian cancer patients. Only one patient (ovarian cancer BRCA wild type) discontinued rucaparib due to an increased ALT or AST (0.3%).

Liver function tests (ALT, AST, bilirubin and alkaline phosphatase) were analyzed to monitor for events of drug-induced liver injury according to Hy's Law laboratory criteria.

One patient with relapsed ovarian cancer in Study CO-338-017, patient 31005-206, was observed to have laboratory values which met criteria for potential Hy's Law, drug-induced liver injury: ALT/AST > 3 x ULN and bilirubin levels > 2 x ULN without evidence of cholestasis, and elevated alkaline phosphatase. The abnormal lab values were noted 14 days after beginning treatment with rucaparib. The patient had documented metastatic disease within the liver at baseline and there was no disease progression documented at that time. Rucaparib was held and the laboratory values decreased. Rucaparib was able to be resumed and the patient remained on rucaparib for a total of 159 days without further LFT abnormality greater than Grade 1.

Reviewer Comment: There were a significant number of ALT and AST elevations observed in the ovarian cancer population. The majority were Grades 1 and 2. In general, the elevations were transient and associated with rucaparib dosing, indicating a likely causal relationship. There were few dose modifications and only one patient required treatment discontinuation, allowing the patients to remain on the study drug. In the potential Hy's law case, the liver function test values rose during the first cycle of rucaparib to the level meeting criteria for Hy's Law. After resuming therapy, subsequent liver enzyme elevations were no more severe than Grade 1 and appeared to be associated temporally with rucaparib dosing. While rucaparib may have the potential to cause drug-induced liver injury, a clear signal for hepatic injury beyond laboratory abnormalities was not demonstrated.

11.4.6. **Safety Analyses by Demographic Subgroups**

Subgroup analyses based on gender was not performed as the study population was entirely (100%) female. Subgroup analyses based on age and race are shown below.

All patients experienced TEAEs, regardless of age. Serious TEAEs were lowest in patients ≥75 years, otherwise rates of serious TEAEs were similar. TEAEs leading to discontinuation, as well as to dose

interruptions or modifications, were higher in patients ≥ 75 years of age, and Grade 3-4 AEs were higher in patients ≥ 65 years of age. The safety profile on rucaparib across age is summarized in Table 36.

Table 36 Overall Summary of TEAEs by Age groups: Safety Population for Patients with Ovarian Cancer (N=377)

	All Ovarian Cancer Patients 600 mg BID			
	Age < 65 Years N = 217	**Age ≥65 to <75 Years N = 119**	**Age ≥75 Years N = 41**	**Age ≥65 Years N = 160**
TEAE[a]	217 (100.0%)	119 (100.0%)	41 (100.0%)	160 (100.0%)
Serious TEAE[a]	59 (27.2%)	36 (30.3%)	9 (22.0%)	45 (28.1%)
≥ Grade 3 TEAE[a]	125 (57.6%)	78 (65.5%)	26 (63.4%)	104 (65.0%)
TEAE with an outcome of death[a]	5 (2.3%)	3 (2.5%)	1 (2.4%)	4 (2.5%)
TEAE leading to discontinuation[a]	32 (14.7%)	25 (21.0%)	12 (29.3%)	37 (23.1%)
TEAE leading to treatment interruption or dose reduction	92 (42.4%)	60 (50.4%)	21 (51.2%)	81 (50.6%)

Source: IR-20161018a

[a] Included events of disease progression.

Reviewer comment:
Though there were fewer TEAEs leading to death in patients ≥ age 75 years, overall, the younger patients, age < 65 years, experienced fewer TEAEs.

The subgroups of races represented in the ovarian cancer safety population were White (80.2%), Asian (5.8%), Black or African American (2.1%) and other/multiple (1.6%). Race was missing from 10% of patients in the demographics dataset. Because of the small numbers in the non-white categories, the TEAEs were assessed by category groupings of White and Non-Whites for analyses purposes. In all TEAE categories, except for TEAEs leading to death, TEAEs were higher in the non-white group. There were no TEAEs leading to death in the non-white group (0/37) and 8/303 (2.6%) in the white group of patients. The safety profile on rucaparib across race is summarized in Table 37.

Table 37 Summary of TEAEs by Race: Safety Population for Patients with Ovarian Cancer (N=340[a])

	All Ovarian Cancer Patients 600 mg BID	
	Non-White (N=37)	**White (N=303)**
TEAE[a]	37 (100%)	303 (100%)
Serious TEAE[a]	13 (35.1)	83 (27.4%)
≥ Grade 3 TEAE[a]	24 (64.9)	182 (60.1%)
TEAE with an outcome of death[a]	0	8 (2.6%)
TEAE leading to discontinuation[a]	8 (21.6)	50 (16.5%)
TEAE leading to treatment interruption or dose reduction	29 (78.4%)	187 (61.7%)

Source: ISS Table 3.4.1 and 3.5.1

[a] 38 (10%) of patients had race missing in the demographics dataset

11.4.7. Specific Safety Studies/Clinical Trials

No specific studies were conducted to evaluate any specific safety concern.

11.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

For a description of carcinogenicity refer to the nonclinical review.

Pediatrics and Assessment of Effects on Growth

This drug was not studied in pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There does not appear to be an overdose or drug abuse potential.

11.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable as no postmarket experience has been obtained.

Expectations on Safety in the Postmarket Setting

No additional specific safety concerns exist regarding subpopulations or use in the post-market setting.

11.4.10. Integrated Assessment of Safety

The safety profile of rucaparib is acceptable for previously treated patients with advanced ovarian cancer. The size of the safety database and duration of rucaparib exposure were sufficient to characterize the safety of rucaparib in the studied patient population for treatment of a serious and life-threatening condition. This is discussed further in section 11.4.2 Review of the Safety Database.

The most significant toxicities included myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Both MDS and AML have been identified occurring with other PARP inhibitors and are AEs of special interest. Within the overall safety population of 409 patients studied for the application, there have been a total of 2 cases of MDS and 1 case of AML diagnosed as of the 60 day safety update. There have been no deaths associated with these cases. Increased monitoring guidelines for cytopenias were

appropriately instituted and recommendations for placement in the Warnings and Precautions section of labeling.

Other notable toxicities included elevated liver function tests and anemia. Two of the most common laboratories abnormalities were elevations (Grades 1-4) in hepatic enzymes ALT (77%) and AST (78%). Though occurring frequently, the majority were Grade 1 and 2 in severity, (64%) in ALT and (74%) in AST. The liver function test abnormalities appear to be drug related and were stabilized or reversed in most cases with drug modification, resulting in only one discontinuation. There was a single case of a patient with liver function abnormalities meeting the criteria for Hy's Law described in section 11.4.5 Analysis of Submission-Specific Safety Issues however this patient's labs improved and they went on to receive further treatment with rucaparib without issue. Given these findings, the risk of liver injury was not included as in the warnings and precautions section of labeling but the frequency of hepatic laboratory abnormalities is conveyed in section 6.

Anemia was the most common occurring AE at 42% across all grades, and 23% ≥ Grade 3 severity. The AE was well managed with dose interruptions and treatment modification guidelines effective in minimizing drug discontinuations.

This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of rucaparib and the experience of the medical community in managing anemia, myelosuppression, and liver function abnormalities. Recommendations for safe and effective use of rucaparib, including monitoring for anemia and myelosuppression, and risk of AML/MDS, will be reflected in labeling and the patient prescribing insert.

The safety and tolerability of rucaparib monotherapy compared with either chemotherapy or chemotherapy plus bevacizumab demonstrates a tolerable and potentially improved toxicity profile. While cross-trial safety comparisons are difficult to make, it is relevant to note that for rucaparib, no ARs rose to the level of requiring a boxed warning, and AML/MDS was the only AR that required description in the Warnings and Precautions section of labeling. This rucaparib safety labeling is very distinct from that of chemotherapies such as bevacizumab which include multiple warnings and precautions and boxed warnings. Therefore, rucaparib will provide an option with an alternative and likely better toxicity profile with the potential to delay chemotherapy for many patients. In summary, the safety profile of rucaparib is acceptable for the intended population.

SUMMARY AND CONCLUSIONS

11.5. Statistical Issues

Study 10 and ARIEL2 were designed to be single-arm, open-label studies with different study objectives, while this NDA review is based on combining patients from different study portions satisfying common disease criteria. The single-arm aspect of the analyses (b) (4) . However, ORR in this clinical context is thought to be reasonably likely to predict clinical benefit and can be assessed in a single-arm trial as tumor response can be attributed to activity of the drug. The discrepancy between the investigator and IRR assessment of ORR was ~12%; however, this discrepancy was not felt to impact the overall interpretability of rucaparib efficacy. The recommendation for accelerated approval takes into account these potential uncertainties. Subsequent trials to confirm clinical benefit are ongoing.

11.6. Conclusions and Recommendations

Ovarian cancer is a disease often diagnosed at advanced stage, and patients routinely undergo successive treatment regimens with a variety of cytotoxic combinations. An important goal for drug development in this patient population is to find safe and effective alternatives to the traditional cytotoxics, to provide clinical benefit and to avoid the additive toxicities of the original regimens. Exploiting a molecular defect can provide a meaningful alternative to cytotoxics, as has been the case in lung cancer and other solid tumors. Rucaparib has been demonstrated to have antitumor efficacy in this application for the treatment of women with advanced ovarian cancer.

This application presented efficacy data from a population of 106 women with advanced ovarian cancer, BRCA mutation in the germline or the tumor, and at least two prior chemotherapy regimens. The population contained women who were considered platinum sensitive, as well as platinum resistant/refractory. Though this application presents an analysis that departs from the presepecified statistical designs of the two efficacy trials that were pooled for this population, the analyses presented are consistent with advice provided by FDA. This advice centered around focusing on a BRCAm population and focused companion diagnostic, rather than awaiting the results of the development of a separate homologous recombination deficiency assay. Though these single-arm trials depended on investigator assessment of progression and duration of response, these assessments were consistent with those performed by blinded independent radiology review, and were further supported by a secondary audit of discrepancies. Based on these assessments, objective response rate (ORR) in the identified efficacy population was 54%, with duration of 9.2 months at median; and, in a non-prespecified, exploratory analysis of patients with platinum-sensitive disease, ORR approached 66%.

Safety of rucaparib was demonstrated in a larger safety population taken from three trials; all 409 patients were treated with the target dose of 600 mg PO BID, 377 of whom had an ovarian cancer diagnoses. In this population, the most significant toxicities are the development of myelodysplastic syndrome/acute myelogenous leukemia, which appear to be a class effect associated with PARP inhibition. Other safety concerns include laboratory abnormalities in liver functions, which were generally low-grade and resulted in treatment discontinuation in only one patient; anemia, which occurred across all grades, and was easily managed.

In summary, the reviewers recommend accelerated approval for rucaparib for the following indication:

> RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.

The safety and efficacy review of the data submitted for rucaparib demonstrate a favorable benefit-risk ratio for the indicated population and contain enough evidence to recommend accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials (ARIEL3 and ARIEL4).

12 Appendices

12.1. Financial Disclosure

Also refer to individual study financial disclosure contained in section**s** 11.2.1 and 11.2.2.

Covered Clinical Studies: ARIEL2 and Study 10

Table 38 Financial Disclosure Summary ARIEL2 and Study 10

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 585		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

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13 Labeling Recommendations

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13.1. Prescribing Information

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Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling** *(As of November 18, 2016)*
Highlights		
Indications and Usage	*See Full Prescribing Information, 1 Indications and Usage.*	*See Full Prescribing Information, 1 Indications and Usage.*
Dosage and Administration	• Recommended dose is 600 mg orally twice daily. (2.2)	FDA added the following information: • Continue treatment until disease progression or unacceptable toxicity. (2.2) • For adverse reactions, consider interruption of treatment or dose reduction. (2.3)
Adverse Reactions	… Most common laboratory abnormalities were increase in creatinine, increase in ALT, increase in AST, decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, decrease in absolute neutrophil count. (6.1)	FDA revised the list of most common laboratory abnormalities to add the incidence rate used to determine inclusion (i.e., 35%).
Use in Specific Populations	• Lactation (b) (4) (8.2)	FDA revised to the following: "• Lactation: Advise women not to breastfeed. (8.2)"
Full Prescribing information		
1 Indications and Usage	Rubraca™ is indicated as monotherapy treatment of (b) (6) patients with deleterious BRCA- (b) (4) (b) (4) who have been treated with two or more chemotherapies. …	FDA revised the indication to reduce the number of clauses, improve readability, and to provide clarity related to appropriate use of the FDA-approved companion diagnostic as follows: "Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-

		approved companion diagnostic for Rubraca."
2 Dosage and Administration *2.2 Recommended Dose*	The recommended dose (b) (4) Rubraca is 600 mg taken twice daily with or without food. Continue treatment until disease progression or unacceptable toxicity. If a patient misses a dose, instruct the patient to (b) (4) next (b) (4) dose. Vomited doses should not be replaced.	FDA revised this subsection to add the route of administration (i.e., "orally"), to clarify the recommended dosage form ["(two 300 mg tablets)"], and to add white space to improve readability.
5 Warnings and Precautions *5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia*	Myelodysplastic syndrome (MDS) was reported in (b) (4) patients with ovarian cancer. The duration of Rubraca treatment prior to the diagnosis of MDS was 57 days. (b) (4) received prior treatment with platinum and other DNA damaging agents. ...	FDA revised the first paragraph in this subsection to record an additional patient diagnosed with AML as submitted to FDA in the safety update. *See Sections 11.4.5 and 11.4.6 of this review for more information.*
6 Adverse Reactions *6.1 Clinical Trials Experience*	(b) (4)	FDA revised the number of patients from (b) (4) to 377 due to pathology confirmation considerations. S*ee Section 11.4.5 of this review for more information*. FDA added information to provide a complete description of the clinical trial database (i.e., "in two open-label, single arm trials"). FDA revised the demographics of the exposed population to include the most clinically relevant patient characteristics from the clinical trial database. FDA revised the adverse

	(b) (4)	reactions that led to dose reduction or interruption based on the FDA safety review. FDA added the most common adverse reactions leading to discontinuation (i.e., fatigue/asthenia (2%). *See Section 11.4.5 in this review for more information.* For Table 2, FDA added "constipation" and "abdominal pain" as adverse reactions. *See Section 11.4.5 in this review for more information.* FDA removed the (b) (4) (b) (4) (b) (4) A footnote to provide the incidence of ALT/AST increase that led to treatment discontinuation as added to Table 3. FDA removed the (b) (4) from labeling.
(b) (4)	(b) (4)	FDA deleted this section.

	(b) (4)	Potential drug-drug interactions are described in Section 12.3. *See Section 10 Clinical Pharmacology in this review for more information.*
8 Use in Specific Populations *8.3 Females and Males of Reproductive Potential*	(b) (4) Rubraca can cause (b) (4) fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Contraception *Females* Advise females of reproductive potential to use effective contraception during treatment (b) (4) and for (b) (4) (b) (4) the final dose (b) (4)	FDA added the following: *"Pregnancy Testing* Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca." FDA revised this subsection to add statements that Rubraca can cause fetal harm when administered to pregnant women and to advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Rubraca.
8 Use in Specific Populations *8.6 Hepatic Impairment*	(b) (4)	FDA revised this subsection to be more concise and to provide the definition of mild hepatic impairment (i.e., total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST).
8 Use in Specific Populations *8.7 Renal Impairment*	(b) (4) No dose	FDA revised this subsection to use the recommended dose for patients with mild and moderate

	adjustment is (b) (4) for patients with mild renal impairment (creatinine clearance [CLcr] (b) (4) mL/min) (b) (4) [*see Clinical Pharmacology (12.3)*] (b) (4)	renal impairment (CrCl= 30 – 89 mL/min, as estimated by the Cockcroft-Gault method).
12 Clinical Pharmacology *12.1 Mechanism of Action*	Rubraca is (b) (4) of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity (b) (4) inhibition of PARP enzymatic activity and (b) (4) of PARP-DNA complexes resulting in (b) (4) DNA damage, apoptosis, and cell death. (b) (4) Rucaparib has been shown to (b) (4)	FDA revised this section to be more consistent with the previously labeled PARP-inhibitor mechanism of action (MoA). FDA removed (b) (4) FDA made other revisions to better reflect the MoA-related activity in tumor cell lines with and without BRCA deficiencies.

	(b) (4)	
12 Clinical Pharmacology *12.2 Pharmacodynamics* Cardiac Electrophysiology	The effects of multiple doses of Rubraca on QTc interval was evaluated in an open-label single-arm study in 56 patients with solid tumors who were administered continuous doses of Rubraca ranging from 40 mg once daily to 840 mg twice daily. (b) (4)	FDA revised this subsection to provide the relationship between the doses tested and the recommended dose for Rubraca [i.e., 40 mg once daily (0.03 times the approved recommended dosage) to 840 mg twice daily (1.4 times the approved recommended dosage)]. FDA revised the QT findings to the following: "The mean QTcF increase from baseline (90% confidence interval [CI]) in population pharmacokinetics estimated 95% percentile Cmax (3019 ng/mL) at steady state of 600 mg rucaparib twice daily was 14.9 msec (11.1-18.7 msec)." *Reviewer Comment: The FDA IRT review team suggested alternative language be used for the concentration-QT analysis due to PK variability, uncertainties of intrinsic/extrinsic factors on drug exposure, and limitations in the QT study design and conduct. See the QT IRT review and Section 11.4.6, Arrhythmias/ QTc Prolongation in this review for more detailed information.*
12 Clinical Pharmacology *12.3 Pharmacokinetics*	Absorption (b) (4)	FDA revised this section to add the mean absolute bioavailability of rucaparib (i.e., 36% with a

	(b) (4)	range from 30% to 45%) and to remove the C_{max} and AUC_{0-12h} information.
	The median Tmax was 1.9 hours, (b) (4)	
	…	FDA revised (b) (4) to "elimination" and added the following information to this subsection: "The apparent clearance ranged from 15.3 to 79.2 L/hour, following continuous 600 mg rucaparib orally twice daily."
	(b) (4)	
	The mean (b) (4) (t1/2) was 17 to 19 hours, following a single dose of rucaparib 600 mg. The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous dose of rucaparib 12 mg to 40 mg.	
	…	FDA revised this subsection to reflect the FDA Clinical Pharmacology reviewer's findings for patients with mild renal impairment (Clcr between 60 and 89 mL/min) and moderate renal impairment (Clcr between 30 and 59 mL/min).
	<u>Specific Populations</u>	
	…	
	Renal Impairment	
	(b) (4)	
	In patients who received rucaparib 600 mg twice daily,	

	those with mild renal impairment (b) (4) showed approximately (b) (4) higher steady-state AUC (b) (4) (b) (4) … …	
14 Clinical Studies	The efficacy of Rubraca was (b) (4) in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rubraca 600 mg twice daily. (b) (4) (b) (4) (b) (4) BRCA mutation status (b) (4) the FoundationFocus CDx*BRCA*™ test (b) (4)	FDA revised this section to provide patient discontinuation criteria (i.e., "until disease progression or unacceptable toxicity") and to clarify that ORRs were assessed by both investigator and independent radiology review (IRR). FDA revised the demographic information by pooling Study 1 and 2 and adding additional information to better clarify the measurement methodology and results for deleterious BRCA mutations as follows: "The median age of the patients was 59 years (range 33 to 84), the majority were Caucasian (78%), and 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had

	(b) (4)	received 3 or more prior lines of chemotherapy. There were 18/106 patients (17%) who had deleterious BRCA mutations detected in tumor tissue and not in whole blood specimens. Tumor BRCA mutation status was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the companion diagnostic FoundationFocus CDxBRCA™ test, which is FDA approved for selection of patients for Rubraca treatment."
	(b) (4)	
	Table 4: Overall Response and Duration of Response in Patients with BRCA-mutant Ovarian Cancer Who Received 2 or More Chemotherapies in Study 1 and Study 2	FDA revised Table 4 to present the pooled efficacy results (b) (4)
	(b) (4)	FDA revised this information to add the IRR results; and platinum-sensitive, platinum-resistant, and platinum-refractory results as follows: "Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation."

13.2. Patient Labeling

- FDA added "Take Rubraca with or without food" to the "***How should I take Rubraca?"*** section of the PPI.
- FDA added stomach-area pain, constipation, and anemia to the ***"What are the possible side effects of Rubraca***?" section of the PPI.

Reviewer Comment: The FDA review team identified another product (Lynparza®) with the same established pharmacologic class and a Medication Guide (MG). The Review Team determined that the Patient Package Insert (PPI) for Rubraca was adequate to disseminate the risk and safety information to patients; and the Rubraca PPI was relatively consistent for similar safety information included in the Lynparza® MG.

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/s/

WILLIAM F PIERCE
11/25/2016

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