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APPLICATION NUMBER:

209115Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 209115
Product Name: Rubraca (Rucaparib) 300 mg tablet, 200 mg tablet

PMR Description: 3141-1 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).

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Rucaparib is being approved under subpart H (accelerated approval); therefore, confirmatory trials are needed to confirm safety and efficacy. These patients have a serious and life-threatening condition with an unmet need for better therapies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ARIEL3, the ongoing randomized, double-blind, placebo-controlled, (b) (4) trial to assess the efficacy of rucaparib maintenance monotherapy in relapsed high-grade serous ovarian cancer patients (b) (4)

(b) (4) who have responded to platinum-based chemotherapy.

This trial will establish the efficacy of rucaparib in maintenance treatment, in an earlier line of therapy than the current accelerated approval.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- ☒ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, double-blind, placebo-controlled, (b) (4) trial to assess the efficacy of rucaparib maintenance monotherapy in improving PFS and/or OS in relapsed high-grade serous ovarian cancer (b) (4) who have responded to platinum-based chemotherapy (study CO-338-014, ARIEL3).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #	209115
Product Name:	Rubraca (Rucaparib) 300 mg tablet, 200 mg tablet
PMR Description: 3141-2	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).
PMR Schedule Milestones:	Final Protocol Submission (ARIEL4): Submitted 06/20/2016
	Interim Report Submission (PFS analysis): 12/2022
	Trial Completion: 6/2024
	Final Report Submission (OS analysis): 12/2024

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Rucaparib is being approved under subpart H (accelerated approval); therefore, confirmatory trials are needed to confirm safety and efficacy in the proposed population: advanced, relapsed BRCAm-associated ovarian cancer. These patients have a serious and life-threatening condition with an unmet need for better therapies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ARIEL4 is a planned multicenter, open-label, randomized trial of rucaparib vs chemotherapy in patients with BRCA-mutated relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. This trial will establish the superiority of single-agent rucaparib over conventional third-line chemotherapy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☒ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Multicenter, open-label, randomized trial of rucaparib vs chemotherapy in patients with BRCA-mutated relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (study CO-338-043, ARIEL4) to establish the superiority of rucaparib over physician's choice chemotherapy in this patient population (study CO-338-043, ARIEL4).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #	NDA 209115
Product Name:	Rucaparib
PMR Description: 3141-4	Complete the ongoing drug-drug interaction trial CO-338-044 and submit the final study report.

PMR Schedule Milestones:	Final Report Submission:	12/2018
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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Inhibition of several CYPs or transporters may cause drug-drug interactions (DDIs). *In vitro*, rucaparib was a reversible inhibitor of CYP1A2, CYP2C19, CYP2C9, and CYP3A, and it was also an inducer of CYP1A2. The ongoing DDI trial CO-338-044 evaluates the effect of rucaparib on the sensitive substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and P-gp. The ongoing DDI study CO-338-044 can help determine whether any dose adjustment for the concomitant use of sensitive substrates of these CYP enzymes and P-gp is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal is to determine whether any dose adjustment for the concomitant use of sensitive substrates of CYP enzymes and P-gp is needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The ongoing drug-drug interaction study CO-338-044 is a Phase 1, open-label, sequential, (b) (4) DDI study to assess the effect of rucaparib (b) (4) on (b) (4) substrates of CYP1A2, CYP2C9, CYP2C19, CYP3A4, and P-gp in patients with advanced solid (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial

- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #	NDA 209115
Product Name:	Rucaparib
PMR Description: 3141-3	Conduct a dedicated PK study in patients with moderate hepatic impairment to determine the appropriate starting dose in patients with moderate hepatic impairment.

PMR Schedule Milestones:

Final Report Submission:

4/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Patients with moderate hepatic impairment are considered a small subpopulation.

(b) (4)

(b) (4)

A dedicated PK study in patients with moderate hepatic impairment should be conducted to determine the appropriate starting dose for this subpopulation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal is to determine the appropriate starting dose of rucaparib for patients with moderate hepatic impairment. A dedicated PK study in patients with moderate hepatic impairment will help determine the appropriate starting dose in this subpopulation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☒ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #	209115
Product Name:	Rubraca (Rucaparib) 300 mg tablet, 200 mg tablet
PMC Description: 3141-5	Submit to FDA the appropriate analytical and clinical validation of a companion diagnostic test that will enable the evaluation of patients' germline BRCA status.
PMC Schedule Milestones:	Final Protocol Submission: 6/2017
	Study Completion 9/2017
	Final Report Submission: 3/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The current companion diagnostic device submitted with the current NDA detects BRCA mutations in tumor tissue and it does not distinguish between germline and somatic mutations. Since the clinical trials for rucaparib used germline mutation status for enrolling only a subset of the population, in order to further define the population for treatment with rucaparib, the sponsor will develop a companion diagnostic device that identifies patients with germline BRCA1/2 mutations in the postmarketing setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the PMC is to develop a test that can identify patients with germline BRCA1/2 mutations for treatment with rucaparib.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- ☒ Other
Analytical and clinical validity of a germline BRCA mutation test

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # NDA 209115
Product Name: Rucaparib

PMC Description: Submit the final study report of ongoing mass balance trial CO-338-045.
3141-6

PMC Schedule Milestones:

Final Report Submission: 9/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The results from the ongoing mass balance trial CO-338-045 will determine the contribution of (b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the ongoing mass balance trial CO-338-045 is to characterize absorption, distribution, metabolism, and elimination pathways of (b) (4) patients. The results from this mass balance trial CO-338-045 will determine the (b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☒ Other

Submission of the final study report of the mass balance trial CO-338-045.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

CHRISTINA D MARSHALL
12/15/2016

KATHERINE M FEDENKO
12/15/2016

13 Labeling Recommendations

13.1. Prescribing Information

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	<i>See Full Prescribing Information, 1 Indications and Usage.</i>	<i>See Full Prescribing Information, 1 Indications and Usage.</i>
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)	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) (4) in patients with deleterious (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) (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. <i>See Sections 11.4.5 and 11.4.6 of this review for more information.</i>
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. <i>See Section 11.4.5 of this review for more information.</i> 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%). <i>See Section 11.4.5 in this review for more information.</i> For Table 2, FDA added “constipation” and “abdominal pain” as adverse reactions. <i>See Section 11.4.5 in this review for more information.</i> FDA removed the (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. <i>See Section 10 Clinical Pharmacology in this review for more information.</i>
8 Use in Specific Populations 8.3 Females and Males of Reproductive Potential	(b) (4) (b) (4), Rubraca can cause (b) (4) fetal harm when administered to a pregnant woman [see <i>Use in Specific Populations</i> (8.1)]. <u>Contraception</u> <i>Females</i> Advise females of reproductive potential to use effective contraception during treatment (b) (4) and for (b) (4) the final dose (b) (4)	FDA added the following: <i>“Pregnancy Testing</i> 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)	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) (b) (4) (b) (4) [see <i>Clinical Pharmacology (12.3)</i>] (b) (4) (b) (4) (b) (4) (b) (4) (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) (b) (4) inhibitor 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) (b) (4) (b) (4) (b) (4) (b) (4) Rucaparib has been shown to (b) (4) (b) (4)	FDA revised this section to be more consistent with the previously labeled PARP-inhibitor mechanism of action (MoA). FDA removed (b) (4) (b) (4) (b) (4) (b) (4) (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 <u>Cardiac Electrophysiology</u>	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).” <i>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.</i>
12 Clinical Pharmacology 12.3 Pharmacokinetics	<u>Absorption</u> (b) (4)	FDA revised this section to add the mean absolute bioavailability of rucaparib (i.e., 36% with a

	(b) (4) The median Tmax was 1.9 hours, (b) (4) ... (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. ... <u>Specific Populations</u> ... <i>Renal Impairment</i> (b) (4) In patients who received rucaparib 600 mg twice daily,	range from 30% to 45%) and to remove the C_{max} and AUC_{0-12h} information. 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.” 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).
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	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) (b) (4) (b) (4) BRCA mutation status (b) (4) the FoundationFocus CDxBRCA™ 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) (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 (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.” FDA revised Table 4 to present the pooled efficacy results (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.”
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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

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 7, 2016

To: Kim Robertson
Regulatory Health Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products

From: Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: RUBRACA™ (rucaparib) tablets, for oral use
NDA 209115

Office of Prescription Drug Promotion comments on proposed
prescribing information (PI) and container labels

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) and proposed container labels for RUBRACA™ (rucaparib) tablets, for oral use as requested by DOP1 in the consult dated June 30, 2016. OPDP's review of the proposed PI is based on the draft PI titled, "10-27-16 FDA revised Rucaparib USPI.docx" sent by electronic mail on October 27, 2016, to OPDP (Kevin Wright) from DOP1 (Sakar Wahby). OPDP comments are listed on the attached PI.

OPDP's review of the proposed container labels are based on the proposed PI. OPDP has no comments for the proposed container labels. The combined OPDP and Patient Labeling Team review of the patient package insert will be provided under a separate cover.

If you have any questions, please feel free to contact, Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

KEVIN WRIGHT
11/07/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 4, 2016

To: Geoffrey Kim, MD
Director
Division of Oncology Products 1 (DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD, BCPS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): Rubraca (rucaparib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209115

Applicant: Clovis Oncology, Inc.

1 INTRODUCTION

On June 23, 2016, Clovis Oncology, Inc. submitted for the Agency's review the final part of the rolling submission of New Drug Application (NDA) 209115 for Rubraca (rucaparib) tablets. The proposed indication is for Rubraca (rucaparib) monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline and somatic BRCA mutations, as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on June 30, 2016 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Rubraca (rucaparib) tablets.

2 MATERIAL REVIEWED

- Draft Rubraca (rucaparib) tablets PPI received on June 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 27, 2016.
- Draft Rubraca (rucaparib) tablets Prescribing Information (PI) received on June 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 27, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
11/07/2016

KEVIN WRIGHT
11/07/2016

LASHAWN M GRIFFITHS
11/07/2016

Clinical Inspection Summary

Date	October 14, 2016
From	Lauren Iacono-Connors, Reviewer
To	Kim J. Robertson, Regulatory Project Manager Sanjeeve Balasubramaniam, Clinical Reviewer Division of Oncology Products 1
NDA #	209115
Applicant	Clovis Oncology, Inc.
Drug	Rucaparib (CO-338)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline BRCA and somatic BRCA mutations, and who have been treated with two or more chemotherapies.
Consultation Request Date	July 7, 2016
Summary Goal Date	October 1, 2016
Action Goal Date	December 16, 2016
PDUFA Date	February 23, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study CO-338-010 and Study CO-338-017 were submitted to the Agency in support of NDA 209115. Four clinical sites, Dr. Amit Oza (Site 020 for Study CO-338-010 and Site 14001 Study CO-338-017), Dr. Anna Tinker (Site 14002 Study CO-338-017), Dr. Robert Coleman, (Site 32005 Study CO-338-017), Dr. Carol A. Aghajanian (Site 32002 Study CO-338-017), and the study sponsor, Clovis Oncology, Inc. (Clovis), of Study CO-338-010 and Study CO-338-017, were selected for audit.

The primary efficacy endpoint for Study CO-338-017, Progress Free Survival (PFS), was verified with the source records generated at the inspected clinical sites. The primary efficacy endpoint for Study CO-338-010 (Part 2A), Objective Response, defined as a best confirmed response of CR or PR, was verified with the source records generated at the inspected clinical site. There were no significant deficiencies. The inspections of Dr. Oza, Dr. Tinker, Dr. Coleman, Dr. Aghajanian and Clovis Oncology, Inc., found no significant deficiencies associated with Study CO-338-010 and Study CO-338-017 conduct.

The data from Study CO-338-010 and Study CO-338-017, submitted to the Agency in support of NDA 209115 appear reliable.

II. BACKGROUND

Clovis seeks approval of Rucaparib (CO-338) for the treatment of patients with advanced ovarian cancer with deleterious BRCA-mutated tumors, inclusive of both germline and somatic BRCA mutations, as detected by an FDA-approved test. This request is based on the results from primarily Study CO-338-017 and a subset of preliminary results from Study CO-338-010.

Study CO-338-017 is a 2-part Phase 2, single-arm, non-randomized, open-label, multicenter study. Part 1 enrolled patients who received ≥ 1 prior platinum-based regimen and had platinum-sensitive disease. Part 2 enrolled patients who received at least 3, but no more than 4, prior chemotherapy regimens. The study treated 315 subjects at 54 clinical centers in North America, Europe, and Australia.

Study Period: Date of first patient entered: October 30, 2013

Data included in the application datalists are for patients in Part 1 and Part 2 enrolled by October 1, 2015, with a visit data cut-off date of February 29, 2016

Primary efficacy endpoint:

- Part 1: Progression Free Survival (PFS), defined as the time from 1+ the number of days from the first dose of study drug to disease progression, as determined by the investigator or death due to any cause, whichever occurs first.
- Part 2: Objective Response Rate (ORR), defined as the proportion of patients with a best response of Complete Response (CR) or Partial Response (PR) using RECIST v1.1 as assessed by the Investigator.

Sponsor's interpretation of primary efficacy outcome: Time to event for PFS. Confirmed CR or PR for ORR.

Objectives of Inspections:

- a. Verify primary efficacy endpoint of PFS as determined by the investigator.
- b. Verify Objective Response, defined as confirmation of a PR or CR event.
- c. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- d. General compliance with the investigational plan.

Study CO-338-010 is a 3-part Phase 1/2 open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered once (QD) or twice daily (BID) for continuous 21-day cycles. Part 2A (Phase 2) enrolled patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a gBRCA mutation who had progressed after at least 2, but no more than 4, prior regimens. Data from patients in Part 2A are included in NDA 209115 and the focus of Study CO-338-010 inspections in support of NDA 209115. A total of 42 patients received at least 1 dose of rucaparib, of whom 9 remained ongoing, as of the November 30, 2015 visit cut-off date. The study is currently ongoing at 7 sites in the United States, United Kingdom, and Israel.

Study Period: Date of first patient entered: December 14, 2011

Data included in the application datalists are for patients in Phase 1 (Part 1) and Phase 2 (Part 2A) with a visit data cut-off date of November 30, 2015.

Primary efficacy endpoint (Part 2A):

- ORR; defined as a best confirmed response of CR or PR as assessed by the investigator using RECIST Version 1.1.
- Duration of Response (DOR); defined as a time to event variable.

Sponsor's interpretation of primary efficacy outcome: Confirmed CR or PR for ORR. Time to event for duration of PR or CR.

Objectives of Inspections:

- a. Verify Objective Response, defined as confirmation of a PR or CR event.
- b. Verify DOR, defined as time between confirmation of a PR or CR event, and disease progression.
- c. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- d. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Amit Oza, M.D. Princess Margaret Hospital 610 University Avenue Toronto ON M5G 2M9	Protocol: CO-338-010 Site Number: 020 Subjects: 6 (Phase 2 [Part 2A]) Protocol: CO-338-017 (Parts 1 and 2) Site Number: 14001 Subjects: 43	September 12-16, 2016	Pending Interim classification: NAI
CI#2: Anna Tinker, M.D. British Columbia Cancer Agency - Vancouver Centre 600 West 10th Avenue Vancouver BC V5Z 4E6	Protocol: CO-338-017 (Parts 1 and 2) Site Number: 14002 Number of Subjects: 21	September 19-22, 2016	Pending Interim classification: NAI
CI#3: Robert Coleman, M.D. University of Texas, MD Anderson Cancer Center Dept. of Gynecology and Oncology 1155 Herman Pressler Drive Unit 1362 Houston TX 77230-1439	Protocol: CO-338-017 Site Number: 32005 Number of Subjects: 26	August 30, 2016 - September 2, 2016	Pending Interim classification: NAI
CI#4: Carol A. Aghajanian, M.D. Memorial Sloan-Kettering Cancer Center 300 East 66th Street New York NY 10065	Protocol: CO-338-017 Site Number: 32002 Number of Subjects: 31	August 22- 26, 2016	Pending Interim classification: NAI
Sponsor: Clovis Oncology, Inc. 499 Illinois Street, Suite 230 San Francisco, California 94158	Protocol: CO-338-017 Site Numbers: 14001, 14002, 32002, 32005 and 11003 Protocol: CO-338-010 Site Numbers: 4, 9, 20, and 60	September 15-27, 2016	Pending Interim classification: NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. CI: Amit Oza, M.D. (Protocol: CO-338-010, Site# 020; Protocol: CO-338-017, Site# 14001)

The inspection reviewed the conduct of two clinical studies (CO-338-010 and CO-338-017). For Study CO-338-010, the site screened six subjects and six were enrolled and treated. At the time of this inspection all six subjects had discontinued due to progressive disease. A record review was done for all subjects. For Study CO-338-017 (Parts 1 and 2 combined), the site screened 53 subjects, 43 were enrolled and 42 were treated. At the time of the inspection 34 subjects had discontinued due to progressive disease, four subjects discontinued due to adverse events, one subject withdrew consent and four subjects remain on study. A detailed record review was done for seven subjects, and a limited review (CA-125 values, and efficacy endpoints) was done for 30 subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209115. Assessment of study oversight and conduct by Dr. Oza included AE reporting practices and general protocol compliance.

The inspection revealed no significant deficiencies. The efficacy endpoint data was verifiable. There was no evidence of under-reporting of AEs.

The data from this Site, associated with Study CO-338-010 and Study CO-338-017 appear reliable.

2. CI: Anna Tinker, M.D. (Protocol: CO-338-017, Site# 14002)

This inspection was issued to review the conduct of one clinical study (CO-338-017). The site screened 36 subjects and 32 were enrolled and treated. At the time of the inspection 22 subjects had discontinued due to progressive disease, two subjects discontinued due to adverse events, three subjects withdrew consent and five subjects remain on study. A detailed record review was done for eleven subjects, and a limited review (CA-125 values, and efficacy endpoints) was done for 14 subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209115. Assessment of study oversight and conduct by Dr. Tinker included AE reporting practices and general protocol compliance.

The inspection revealed no significant deficiencies. The efficacy endpoint data was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 14002, associated with Study CO-338-017 appear reliable.

3. CI: Robert Coleman, M.D. (Protocol: CO-338-017, Site# 32005)

This inspection was issued to review the conduct of one clinical study (CO-338-017). The site screened 37 subjects and 26 were enrolled and treated. At the time of the inspection all 26 subjects had completed the study. A record review was done for ten subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209115. Assessment of study oversight and conduct by Dr. Coleman included AE reporting practices and general protocol compliance.

The inspection revealed no significant deficiencies. The efficacy endpoint data was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 32005, associated with Study CO-338-017, appear reliable.

4. CI: Carol A. Aghajanian, M.D. (Protocol: CO-338-017, Site# 32002)

This inspection was issued to review the conduct of one clinical study (CO-338-017). The site screened 31 subjects and 31 were enrolled and treated. At the time of the inspection 15 subjects had completed the study, three were ongoing and the remaining 13 were discontinued. A record review was done for all 31 subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209115. Assessment of study oversight and conduct by Dr. Aghajanian included AE reporting practices and general protocol compliance.

The inspection revealed no significant deficiencies. The efficacy endpoint data was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 32002, associated with Study CO-338-017, appear reliable.

5. Sponsor: Clovis Oncology, Inc.

The inspection focused on the sponsor's control, oversight, and management of Study CO-338-017 and Study CO-338-010. Monitoring records were reviewed from five clinical sites. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs, SAEs, and protocol deviations were reviewed for five sites. There were no major issues. Clovis maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs.

The data from this sponsor, associated with Study CO-338-017 and Study CO-338-010, submitted to the Agency in support of NDA 209115, appear reliable.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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CC:

Central Doc. Rm. NDA #209115
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DOP1/Clinical Team Leader/Julia Beaver
DOP1/Project Manager/Kim J. Robertson
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OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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

/s/

LAUREN C IACONO-CONNORS
10/14/2016

KASSA AYALEW
10/14/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 209115
Brand Name	Rubraca™
Generic Name	Rucaparib
Sponsor	Clovis Oncology, Inc.
Indication	Monotherapy treatment of advanced ovarian cancer
Dosage Form	Tablet
Drug Class	Poly (ADP-ribose) polymerase (PARP) inhibitor
Therapeutic Dosing Regimen	600 mg orally twice daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not identified
Submission Number and Date	SDN 003; 23 Jun 2016
Review Division	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

QTc prolongation effect of rucaparib was observed in this QT study. There was a trend for greater lengthening of QTcF with increased dose as shown in Table 1. A significant relationship between Δ QTcF and rucaparib concentrations was observed (with a slope estimate of 3.9 ms/(μ g/ml), $p=0.02$). At the median C_{max} in ovarian cancer patients treated with Rubraca 600 mg twice daily, clinically relevant QTc prolongation exceeding 10 ms is expected.

ECGs were collected in Part 1 (Phase I) of this 3-part, phase I/II, open-label, safety, pharmacokinetic, and preliminary efficacy study in patients with advanced solid tumor. Part 1 (Phase I) of the study is an open-label, dose-escalation design with ten cohorts, which consist of rucaparib 40 mg QD, 80 mg QD, 160 mg QD, 300 mg QD, 500 mg QD, 240 mg BID, 360 mg BID, 480 mg BID, 600 mg BID, and 840 mg BID groups. Food effect evaluation was conducted in 9 patients (3 in 40 mg QD group and 6 in 300 mg QD group). A total of 56 patients were in the ECG Population of Part 1 (Phase I), 55 of the 56 patients had data available for the analyses of change from baseline. The intended therapeutic dose, 600 mg BID, and the maximal 840 mg BID doses were listed as separate groups for analyses, but the two doses in food effect evaluation period, 40 to 500 mg QD doses, and 240 to 480 mg BID doses were pooled together as food effect cohort, 40 -500

mg QD group and 240 – 480 mg BID group, respectively. Overall summary of findings is presented in Table 1.

Table 1: Dose-Response for the Largest Mean Changes in Δ QTcF (Cycle 1 Day 15 of Different Rucaparib Groups, FDA Analysis)

				QTcF (ms)		Δ QTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
40 - 500 mg QD	1	15	2	23	414.6 (11.7)	5.9 (16.2)	(-0.1, 11.8)
240 - 480 mg BID	1	15	2	18	426.0 (17.9)	12.8 (11.2)	(8.2, 17.4)
600 mg BID	1	15	2	7	423.0 (27.7)	14.0 (9.9)	(6.8, 21.3)
840 mg BID	1	15	2	3	422.3 (8.1)	26.2 (10.6)	(8.4, 44.1)
Overall (Food Effect Part Excluded)	1	15	2	51	420.2 (17.1)	10.7 (14.2)	(7.4, 14.1)

*Patients in the food effect cohort ingested their first dose of rucaparib in a fasted condition on Day -7, followed by their second dose of rucaparib in a fed (high-fat meal) condition on Day 1 of Cycle 1.

The suprathreshold dosing regimen (840 mg BID) produces mean C_{max} values 1.25-fold the mean C_{max} for the therapeutic dosing regimen (600 mg BID) at day 15 (steady state). The impact of age, race, hepatic and renal impairment, effect of genotype and drug interactions is being evaluated. Based on the positive concentration-QTc relationship, larger QTc prolongation is expected in subjects with intrinsic/extrinsic factors that significantly increase drug exposure.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer's Comment: Because of the PK variability, the uncertainties of impacts of intrinsic/extrinsic factors on drug exposure, and the limitation of the study design and conduct (e.g., food was not controlled in the ECG monitoring study etc.), we don't consider that the actual number of (b) (4) ms with 90% confidence interval of (b) (4) ms is able to reflect the QTc prolongation precisely. We proposed the following labeling language which is a suggestion only. We defer final labeling decisions to the Division.

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)



3 BACKGROUND

3.1 PRODUCT INFORMATION

Rucaparib is a potent small molecule inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play critical roles in DNA repair. Rucaparib also has biochemical activity against other PARP family members, including tankyrase (TNKS) and 2 (TNKS2).

3.2 MARKET APPROVAL STATUS

Rucaparib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of rucaparib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT has agreed to the sponsor's proposal under IND 106289 that no additional QT study was required for this product and asked for this study report to be submitted for further review. The sponsor submitted the study report CO-338-010 for rucaparib, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

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

4.2.2 Protocol Number

CO-338-010

4.2.3 Study Dates

This is a 3-part, phase I/II, open-label, safety, pharmacokinetic, and preliminary efficacy study. The study is ongoing. The date of the first patient enrollment was 14 Dec 2011.

Data cut-off date for different parts:

- Part 1 (Phase I): 30 Nov 2015
- Part 2A (Phase II): 30 Nov 2015
Part 2B (Phase II): It was at initial stages of enrollment at the time of this report.
- Part 3 (Phase II): 10 Dec 2015

Patients enrolled into either Part 1, or Part 2, or Part 3 of the study, meaning patients were not allowed to enroll into multiple parts.

The ECG analyses were from data collected in Part 1 (Phase I) of the study.

4.2.4 Objectives

The primary objectives of Part 1 of the protocol 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);
- To characterize the pharmacokinetic (PK) profile of oral rucaparib when administered as a continuous daily dose.

One of the secondary objectives of Part 1 of the protocol was:

- To evaluate the effects of oral rucaparib on the QT/QTc interval measured by electrocardiogram (ECG).

One of the exploratory objectives of Part 1 of the protocol was:

- To explore the relationship between the PK of oral rucaparib and the potential changes in the QT/QTc interval.

4.2.5 Study Description

4.2.5.1 Design

Part 1 (Phase I) was an open-label, dose-escalation design with ten cohorts.

Oral rucaparib was administered under fasted condition once or twice daily for continuous 21-day cycle(s) in patients with advanced solid tumors. Patients in Part 1 were initially treated in a Dose-escalation Evaluation Period (Cycle 1) and could then continue to receive treatment in an optional Treatment-extension Period (Cycle 2 and beyond). Patients had baseline evaluation on Day -1 and began treatment on Day 1 of Cycle 1.

There was a food effect evaluation period from Day -7 prior to the first treatment Day 1 in Cycle 1 for 9 patients included in the food effect evaluation. These patients had their baseline evaluation on Day -8 and began treatment on Day -7 of Cycle 1. For these patients, the Cycle 1 duration was 28 days. Patients in the food effect cohort ingested their first dose of rucaparib in a fasted condition on Day -7, followed by their second dose of rucaparib in a fed (high-fat meal) condition on Day 1 of Cycle 1. Food effect PK evaluation was conducted at rucaparib dose levels of 40 mg QD (n=3) and 300 mg QD (n=6).

At the time of ECG analyses, ECG data was available for up to 22 cycles in the patient with the longest treatment duration.

4.2.5.2 Controls

Neither placebo nor positive (moxifloxacin) controls were used.

4.2.5.3 Blinding

The study was open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Ten rucaparib dose levels were administered in Part 1 (Phase I):

- 40 mg QD (assessment of food effect was conducted in 3 patients)
- 80 mg QD
- 160 mg QD
- 300 mg QD (assessment of food effect was conducted in 6 patients)
- 500 mg QD
- 240 mg BID
- 360 mg BID
- 480 mg BID
- 600 mg BID
- 840 mg BID

Dose reductions were not permitted during Cycle 1 of Part 1.

4.2.6.2 Sponsor's Justification for Doses

This is a dose-escalation trial.

Reviewer's Comment: Seven subjects received the potential therapeutic dose (600 mg b.i.d.) and three subjects received the highest tested dose (840 mg b.i.d.). Influence of intrinsic/extrinsic factors on rucaparib exposure is under evaluation.

4.2.6.3 Instructions with Regard to Meals

All patients except those in the food-effect PK portions received oral rucaparib either on an empty stomach or with food. See Section 4.2.6.1.

Reviewer's Comment: No substantial food effect on rucaparib absorption. However, different food procedure may confound the ECG results.

4.2.6.4 ECG and PK Assessments

ECGs were obtained at the following time points:

- Screening (all patients):
- Cycle 1 Day -8 (patients in food effect cohorts only): at time point equivalent to estimated postdose T_{max}, ie approximately 2 hrs post-dose of dose to be administered the following day.
- Cycle 1 Day -7 (patients in food effect cohorts only): at 2 and 7 hrs postdose
- Cycle 1 Day -1 (all patients): at time point equivalent to estimated postdose T_{max}, ie approximately 2 hrs post-dose of dose to be administered the following day.
- Cycle 1 Day 1 (all patients): at 2 and 7 hrs postdose
- Cycle 1 Day 15 (all patients): at 2 and 7 hrs postdose
- Cycle 1 Day 22/Cycle 2 Day 1 (all patients): any time prior to dosing
- Cycle 2+ Day 1 (all patients): any time prior to dosing

PK samples were collected predose (any time on Day 1; 5-10 min prior to dosing on Day 15) and at 15 ($\pm$ 2) min, 30 ($\pm$ 3) min, 1 hr ($\pm$ 5 min), 1.5 hrs ($\pm$ 5 min), 2.5 hrs ($\pm$ 5 min), 4 hrs ($\pm$ 15 min), 6 hrs ($\pm$ 15 min), 8 hrs ($\pm$ 15 min), 10 hr ($\pm$ 30 min), and 24 hrs ($\pm$ 30 min) postdose on Days 1 and 15 of Cycle 1.

Reviewer's Comment: Acceptable.

4.2.6.5 Baseline

Baseline is defined as the mean of the values of the triplicate ECGs from Day -1 prior to the first day of dosing in Cycle 1 except in the food effects cohorts where the baseline is the mean of the values on Day -8.

4.2.7 ECG Collection

Standard 12-Lead ECGs, 10 seconds in duration, > 2 minutes apart, were obtained in triplicates, with patients resting for 5 minutes prior to ECG recording.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 56 patients (51 females and 5 males) were in the ECG population. The average age (SD) of the 56 patients was 50.3 (11.6) years, ranging from 21 years to 71 years. The majority of the 56 patients (49/56, 87.5%) were White, 4 patients (4/56, 7.1%) were Black or African American, and 3 patients (3/56, 5.4%) were Asian.

One patient (10101) had no baseline evaluation and thus was excluded from analyses of change from baseline. PK evaluations from 54 patients were available in the dataset.

4.2.8.2 Statistical Analyses

4.2.8.2.1 By-time Analysis

Overall, increases of mean QTcF were seen at most observations for rucaparib dose levels above 160 mg QD. There was an apparent trend for greater increases with rising dose. Where multiple timepoint observations were available, higher values of change of QTcF were seen early after dosing. Thus, during Cycle 1 on Day 1, except for the highest dose, change of QTcF was higher at Hour 2 compared to Hour 7. Higher values of QTcF change were seen for all doses on Day 15 of Cycle 1 at Hour 2 compared to Hour 7. Further, values on Day 15 for BID doses were nearly uniformly higher than on Day 1, while those for QD dosing were variable. No pattern was evident for increasing QTcF elevation with prolonged dosing beyond Cycle 1.

The maximum single value of mean change of QTcF from Baseline, 32.2 msec, was seen for the rucaparib 500 mg QD dose group during an unscheduled ECG. Other than for the unscheduled ECGs, the maximum mean value was 24.7 msec in Cycle 7 for the rucaparib 600 mg BID dose group. In both cases for these maximal values, a single patient's observations represented each mean. On Days 1 and 15 of Cycle 1, the mean values for the rucaparib 600 mg BID group were consistently lower, by about half, as compared to the highest dose group.

4.2.8.2.2 Assay Sensitivity

Not Applicable.

4.2.8.2.3 Categorical Analysis

No patient had QTcF > 450 ms in the once daily groups and the 840 mg BID group, but 33, 13, 22, and 29 percent of patients had QTcF >450 ms in the 240 mg BID, 360 mg BID, 480 mg BID, and 600 mg BID groups, respectively. Thirteen percent of patients in the 360 mg BID group had QTcF >480 ms, and no patient in other groups had QTcF >480 ms. No patient had QTcF >500 ms.

Forty, 22, 25, 13, 22, and 67 percent of patients had change from baseline in QTcF (Δ QTcF) >30 ms in the 40 mg QD, 300 mg QD, 500 mg QD, 360 mg BID, 480 mg BID, and 840 mg BID groups, respectively. There were no patients who had Δ QTcF >30 ms in other groups. Twenty-five percent of patients had Δ QTcF >60 ms in the 500 mg BID group only; patients in other groups had no Δ QTcF >60 ms (source: cardiac safety report for study CO-338-010, Table 9, page 28).

4.2.8.3 Safety Analysis

In part 1 (Phase I), 3 of the 56 patients (5.4%) had treatment emergent adverse events (TEAEs) with death as an outcome. There was 1 death each in the 160 mg QD, 240 mg BID, and 480 mg BID groups. All 3 deaths were due to malignant neoplasm progression and were considered not related to rucaparib.

Twenty-one of the 56 patients (37.5%) had treatment-emergent serious adverse events (SAEs), but the SAEs were considered related to rucaparib only in 3 patients (5.4%). Atrial fibrillation was reported in 1 patient in the 40 - 500 mg QD group.

Fifty-five of the 56 patients (98.2%) experienced at least 1 TEAE; the TEAEs were considered related to rucaparib in 40 patients (71.4%). No patient had treatment related TEAEs that led to rucaparib discontinuation, while 11 (19.6%) patients experienced treatment-related TEAEs that led to dose reduction.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

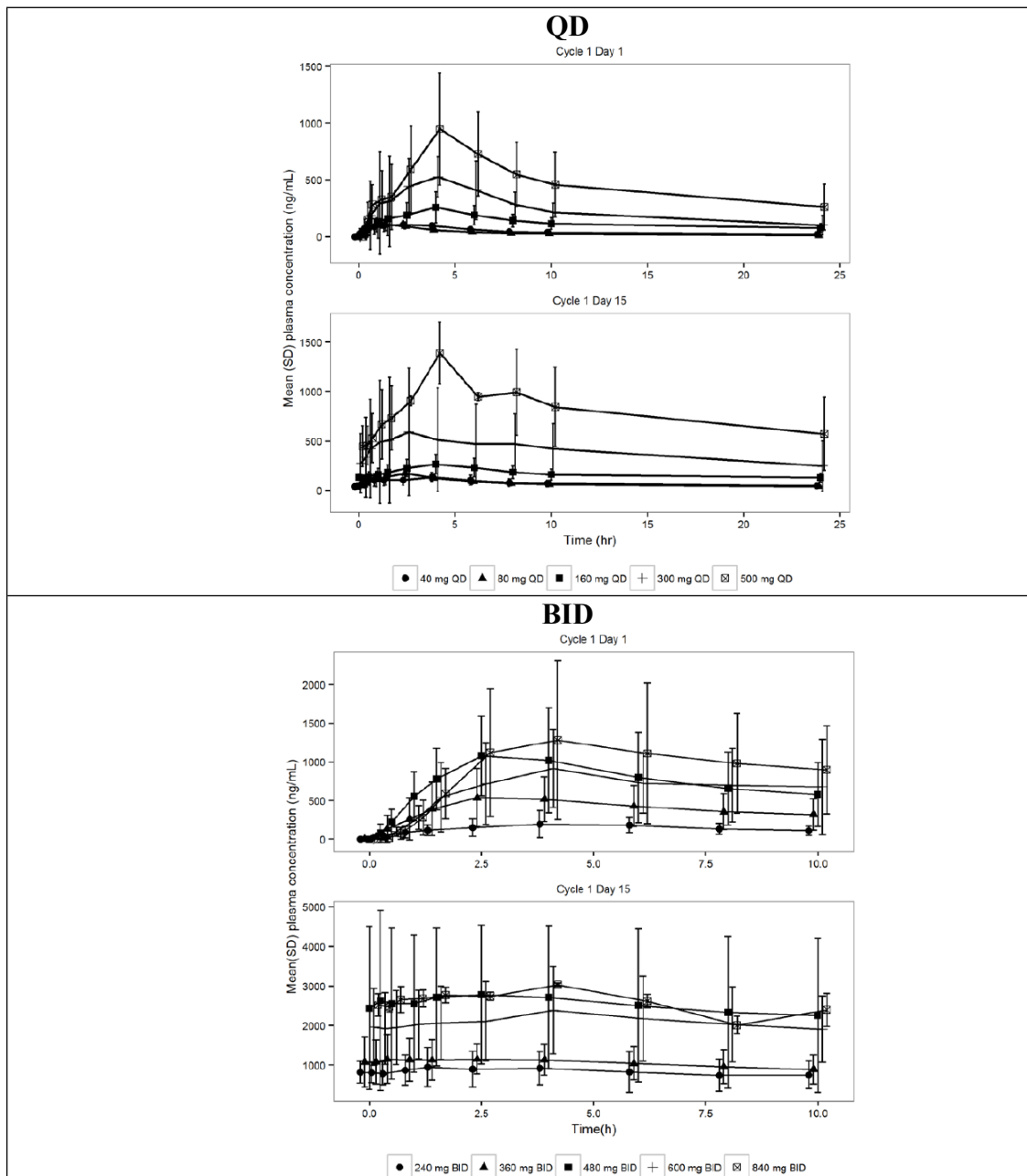
The PK results are presented in Table 2 and Figure 1. Approximate dose-linear PK at steady state following 40-500 mg daily (QD) and 240-840 mg BID as tested by linear regressions of log-transformed exposure and dose i.e., $\text{Log(PK)} = \beta_0 + \beta_1 \times \text{Log(dose)}$ and β_1 is estimated as 1. The accumulation at steady state following a BID dosing schedule was in the range of 2.6 to 4.9 for C_{max}, 3.5 to 6.2 for AUC_{last}, and 1.47 to 5.44 for AUC₀₋₁₂. The accumulation following a BID dosing schedule was approximately twice that of the QD dosing schedule.

Table 2: Single Dose and Steady State Plasma PK Parameters of Rucaparib following QD or BID Administration (Part 1 Dose Escalation)

Dosage	N	Day	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-τ} (ng·hr/mL)	CL _{ss} /F (L/hr)	R _{AUC}	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)	1,810 (44)	26.7 (59)	1.68 ^b	25.7 (23)
40 mg QD (food effect)	3	-7 (fasted)	77.9 (60)	4 (2.5-4.05)	741 (78)	NR	NA	10.6 (50)
		1 (fed)	64.8 (63)	2.55 (1-4.08)	794 (68)	NR	NA	12.6 (42)
		15	129 (62)	4 (1-4.03)	1050 ^a	NR	NR	9.2 ^b
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)	1,740 (20)	47.5 (23)	2.33 (42)	19.5 ^b
160 mg QD	4	1	261 (51)	4.0 (4-6.05)	3,050 (51)	NR	NA	19.9 (21)
		15	288 (29) ^c	3.75 (2.5-4) ^c	4,110 (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)	5,740 (38)	NR	NA	15.2 (72)
		15	693 (76)	2.53 (2.5-8)	9,610 (83)	46.7 (63)	1.6 (53)	29.8 ^b
300 mg QD (food effect)	6	-7 (fasted)	415 (46)	4.09 (2.5-24.22)	5,320 (47)	NA	NA	23.5 (46) ^d
		1 (fed)	502 (75)	5.95 (2.53-10)	6,890 (54) ^e	NA	NA	17.4 (34) ^c
		15	727 (79) ^e	2.47 (1.08-6) ^e	13,300 (106) ^c	NR	NR	20 (68) ^c
500 mg QD	3	1	949 (52)	4 (4-4)	11,000 (61)	NR	NA	15.0 (32)
		15	1390 (23)	4 (4-4.17)	19,900 (41)	27.8 (35)	1.94 (17)	20.8 (38)
240 mg BID	3	1	219 (72)	6 (4.05-6)	2,800 ^a	NR	NA	NR
		15	971 (49)	1.5 (1-4)	10,700 ^b	27.3 ^b	5.44 ^a	
360 mg BID	8	1	666 (58)	3.23 (1.5-6)	4,860 (58) ^f	NR	NA	
		15	1,300 (43) ^f	3.3 (0-6.33) ^f	9,430 ^b	40.4 ^b	4.08 ^b	
480 mg BID	9	1	1,150 (57)	2.5 (1.5-4)	8,810 (63) ^g	NR	NA	
		15	3,170 (69) ^g	1.51 (0-6) ^g	26,300 (73) ^f	26.2 (63) ^f	3.97 (38) ^e	
600 mg BID	7	1	1,030 (61)	4 (2.42-10)	7,200 (66) ^d	NR	NA	
		15	2,420 (45)	4 (2.53-10)	21,400 (61) ^d	58.6 (123) ^d	3.23 (66) ^d	
840 mg BID	3	1	1,380 (69)	4 (2.5-8)	13,200 ^b	NR	NA	
		15	3,030 (1) ^b	4.04 (4-4.07) ^b	29,000 ^a	29 ^a	1.47 ^a	

Sources: Clinical Study Report for Co-338-010, Page 108

Figure 1: Rucaparib Plasma Concentration versus Time by Dose Level (Part 1, excluding Food-effect Cohort, Linear Scale)



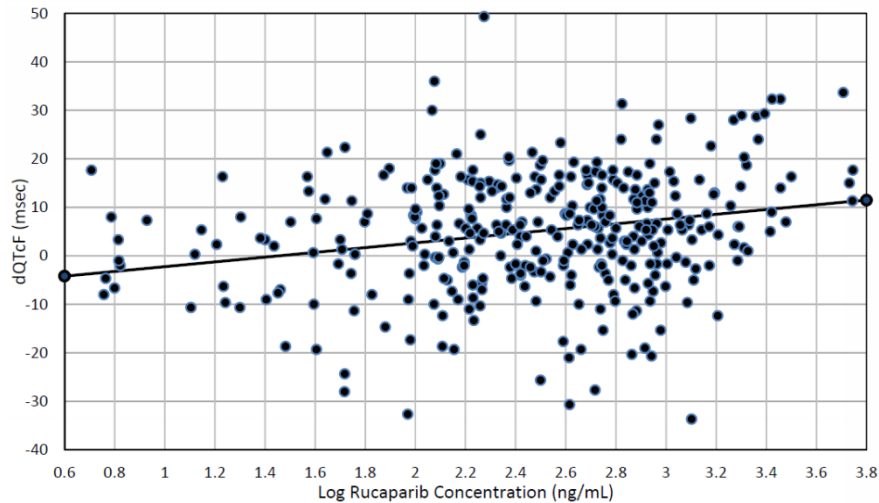
Sources: Clinical Study Report for Co-338-010, Page 106-107

4.2.8.4.2 Exposure-Response Analysis

Values of concentration of rucaparib for individual patients were matched with values of change of QTcF from baseline at the same timepoint. Concentration values for blood drawn at 1.5 and 2.5 hours postdose were averaged to match the ECG 2-hour postdose for Cycle 1 Day 1 and Day 15; and, similarly, values at 6 and 8 hours postdose were averaged to match the 7-hour ECG. Increasing rucaparib concentration was associated with increasing values of change of QTcF from baseline (Figure 2). The mean change of

QTcF at values of concentration corresponding to the various quintiles in the study population was estimated in Table 3. At the maximum value of concentration of rucaparib, the mean change of QTcF from Baseline was 11.3 msec.

Figure 2: Changes from Baseline in QTcF vs. Log Rucaparib Concentration ($y = -7.1 + 4.92 \times \log\text{Conc}$, Slope $p\text{-value} < 0.001$)



Sources: Cardiac Safety Report for Co-338-010, Page 30

Table 3: Mean Change of QTcF from Baseline at Various Concentration of Rucaparib

Concentration Value	Concentration (ng/mL)	Mean Change from Baseline (msec)
Minimum	5.10	-3.7
20%	112.0	2.9
40%	236.5	4.5
60%	515.0	6.2
80%	875.0	7.3
Maximum	5565.0	11.3

Source: Cardiac safety report for study CO-338-010, Table 11, page 30

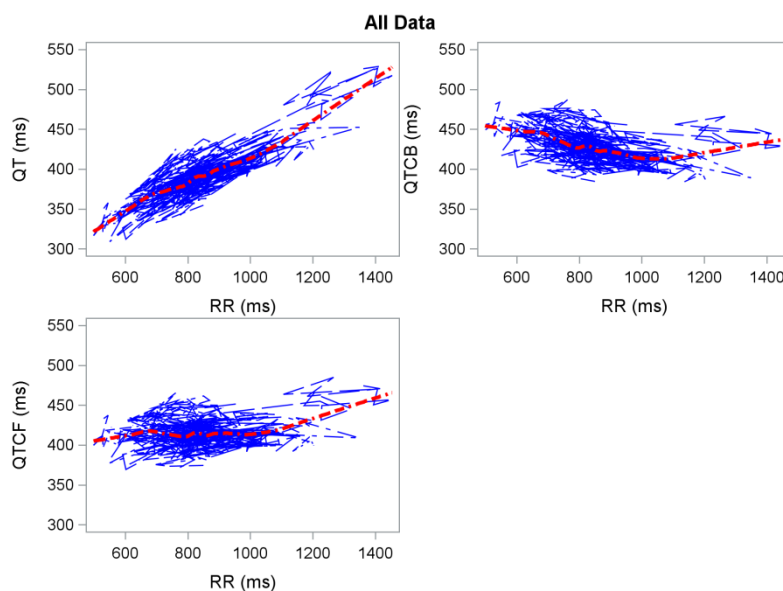
Reviewer's comments: Independent analyses for the relationship between ΔQTcF and rucaparib concentrations were conducted by the reviewer (Figure 5). The linear mixed-effect model with intercept was able to fit the data better (based on the AIC value) compared to the log-linear model as proposed by the sponsor. A significant relationship between ΔQTcF and rucaparib concentrations was observed (with a slope estimate of 3.9 ms/($\mu\text{g}/\text{mL}$), $p=0.02$).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 3. This statistical reviewer used QTcF for the primary statistical analysis.

Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Rucaparib

The primary endpoint is the mean change from baseline in QTcF (Δ QTcF). The descriptive statistics are listed in the following tables.

Table 4: Analysis Results of Δ QTcF for Food Effect Cohort (Rucaparib 40 mg QD and 300 mg QD)

				QTcF (ms)		Δ QTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
Food Effect Cohort	1	-7 (fasted)	2	9	412.5 (14.3)	13.6 (4.5)	(10.8, 16.4)
			7	9	401.9 (15.4)	3.0 (8.5)	(-2.3, 8.2)
		-1	.	9	405.6 (13.3)	6.6 (14.0)	(-2.1, 15.3)

				QTcF (ms)		ΔQTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
		1 (fed)	2	9	403.8 (11.5)	4.8 (7.4)	(0.2, 9.4)
			7	9	404.2 (15.1)	5.2 (8.0)	(0.2, 10.2)

Table 5: Analysis Results of ΔQTcF for Different Rucaparib Groups

				QTcF (ms)		ΔQTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
40 - 500 mg QD	1	1	2	17	419.5 (15.2)	6.9 (15.0)	(0.4, 13.5)
			7	16	411.4 (14.9)	-3.0 (11.3)	(-8.2, 2.1)
		15	2	23	414.6 (11.7)	5.9 (16.2)	(-0.1, 11.8)
			7	23	409.4 (11.9)	1.1 (12.0)	(-3.4, 5.5)
		22	.	4	405.0 (4.9)	-4.2 (18.9)	(-26.4, 18.1)
	2 - 22	1	.	21	409.6 (10.6)	5.4 (12.4)	(3.7, 7.2)
240 - 480 mg BID	1	1	2	19	418.1 (17.6)	3.1 (12.5)	(-1.9, 8.1)
			7	20	414.5 (19.5)	0.7 (12.0)	(-4.0, 5.3)
		15	2	18	426.0 (17.9)	12.8 (11.2)	(8.2, 17.4)
			7	18	421.2 (19.0)	8.0 (9.6)	(4.1, 11.9)
		22	.	1	392.7	16.7	
	2 - 22	1	.	17	425.6 (19.9)	6.8 (12.1)	(4.7, 8.9)
600 mg BID	1	1	2	7	415.5 (29.7)	6.6 (6.7)	(1.7, 11.5)
			7	7	413.9 (26.2)	5.0 (6.5)	(0.2, 9.7)
		15	2	7	423.0 (27.7)	14.0 (9.9)	(6.8, 21.3)
			7	7	418.2 (23.7)	9.2 (7.0)	(4.1, 14.4)
		22	.	1	421.0	-8.0	
	2 - 22	1	.	6	427.8 (19.8)	13.3 (8.2)	(10.5, 16.0)
840 mg BID	1	1	2	3	407.0 (16.5)	10.9 (5.5)	(1.6, 20.2)
			7	3	415.0 (18.1)	18.9 (12.7)	(-2.5, 40.3)
		15	2	3	422.3 (8.1)	26.2 (10.6)	(8.4, 44.1)

				QTcF (ms)		ΔQTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
			7	3	416.1 (6.3)	20.0 (11.2)	(1.1, 38.9)
		22	.	1	426.3	11.3	
	2 - 22	1	.	3	412.7 (9.4)	12.8 (11.0)	(6.0, 19.6)

Table 6: Analysis Results of ΔQTcF for Rucaparib (Overall)

				QTcF (ms)		ΔQTcF (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
Overall (Food Effect Part Excluded)	1	1	2	46	417.5 (18.6)	5.5 (12.4)	(2.4, 8.6)
			7	46	413.3 (18.5)	1.3 (12.1)	(-1.7, 4.3)
		15	2	51	420.2 (17.1)	10.7 (14.2)	(7.4, 14.1)
			7	51	415.2 (16.8)	5.8 (11.5)	(3.1, 8.6)
		22	.	7	408.6 (11.9)	0.5 (16.4)	(-11.5, 12.5)
	2 - 22	1	.	47	417.1 (17.4)	6.9 (12.1)	(5.7, 8.2)

The largest mean change from baseline in QTcF (ΔQTcF) was 26.2 ms, which occurred at 2 hours after dose on Day 15 of Cycle 1 in the 840 mg BID group. However, this number needs to be interpolated with caution because there is only 3 subjects in the 840 mg BID group. QTcF increasing effect was evident at above 240 mg BID dose level. There was a trend of greater ΔQTcF with rising dose. At above 240 mg BID dose level, ΔQTcF on Day 15 was generally higher than that of Day 1 in Cycle 1.

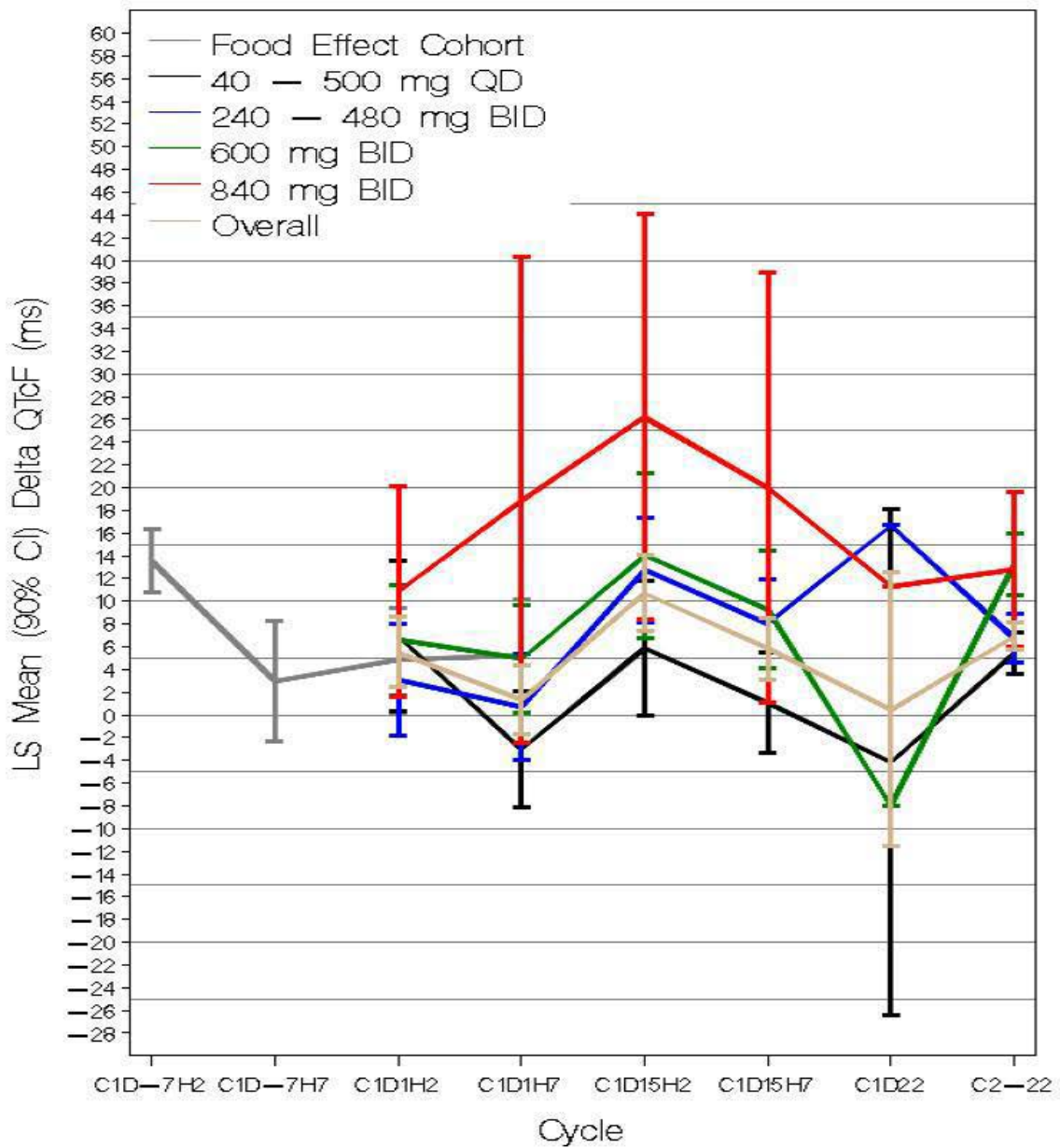
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for different rucaparib dose groups.

Figure 4: Mean Δ QTcF by Rucaparib Group



5.2.1.4 Categorical Analysis

Table 7 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 and 500 ms. No subject's QTcF was above 500 ms.

Table 7: Categorical Analysis for QTcF

Treatment Group	Total N		QTcF $\leq$ 450 ms		450<QTcF $\leq$ 480 ms		480<QTcF $\leq$ 500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	55	55	53 (96.4%)	53 (96.4%)	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
40 - 500 mg QD	26	264	26 (100%)	264 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
240 - 480 mg BID	20	168	17 (85.0%)	155 (92.3%)	2 (10.0%)	12 (7.1%)	1 (5.0%)	1 (0.6%)
600 mg BID	7	55	5 (71.4%)	47 (85.5%)	2 (28.6%)	8 (14.5%)	0 (0.0%)	0 (0.0%)
840 mg BID	3	22	3 (100%)	22 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 8 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 8: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Δ QTcF $\leq$ 30 ms		30< Δ QTcF $\leq$ 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
40 - 500 mg QD	25	258	20 (80.0%)	252 (97.7%)	5 (20.0%)	6 (2.3%)
240 - 480 mg BID	20	168	17 (85.0%)	163 (97.0%)	3 (15.0%)	5 (3.0%)
600 mg BID	7	55	7 (100%)	55 (100%)	0 (0.0%)	0 (0.0%)
840 mg BID	3	22	1 (33.3%)	19 (86.4%)	2 (66.7%)	3 (13.6%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 9 and Table 10. Small HR decreasing

effect was observed at most time points. No trend was observed for the effect of rucaparib on HR changes.

The outlier analysis results for HR are presented in Table 11.

Table 9: Analysis Results of Δ HR for Food Effect Cohort (Rucaparib 40 mg QD and 300 mg QD)

				HR (ms)		Δ HR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
Food Effect Cohort	1	-7 (fasted)	2	9	63.1 (8.7)	-5.6 (4.2)	(-8.1, -3.0)
			7	9	65.9 (11.1)	-2.7 (5.1)	(-5.9, 0.4)
	1 (fed)	-1	.	9	68.2 (11.0)	-0.4 (7.7)	(-5.2, 4.3)
			2	9	71.9 (13.2)	3.3 (9.4)	(-2.5, 9.1)
			7	9	75.4 (16.3)	6.8 (13.1)	(-1.3, 14.9)

Table 10: Analysis Results of Δ HR for Different Rucaparib Groups

				HR (ms)		Δ HR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
40 - 500 mg QD	1	1	2	17	75.9 (16.1)	-4.2 (8.6)	(-8.0, -0.5)
			7	16	79.4 (16.0)	1.0 (10.9)	(-3.9, 6.0)
			2	23	71.3 (16.1)	-3.0 (11.1)	(-7.0, 1.1)
			7	23	77.6 (13.3)	3.3 (9.1)	(0.0, 6.7)
			.	4	88.4 (25.6)	4.2 (4.1)	(-0.6, 9.0)
	2 - 22	1	.	21	69.9 (8.9)	-3.1 (8.9)	(-4.4, -1.9)
240 - 480 mg BID	1	1	2	19	77.5 (13.1)	-5.5 (12.0)	(-10.2, -0.7)
			7	20	80.7 (12.3)	-1.3 (9.6)	(-5.0, 2.4)
			2	18	73.5 (15.5)	-7.9 (10.0)	(-12.0, -3.8)
			7	18	76.7 (14.7)	-4.7 (9.1)	(-8.4, -1.0)
			.	1	95.0	-2.7	
	2 - 22	1	.	17	69.9 (14.8)	-6.9 (9.0)	(-8.5, -5.4)
600 mg BID	1	1	2	7	73.0 (10.1)	-5.3 (11.2)	(-13.5, 2.9)

				HR (ms)		ΔHR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
			7	7	81.6 (16.1)	3.3 (6.4)	(-1.4, 8.0)
		15	2	7	75.8 (13.2)	-2.5 (10.6)	(-10.3, 5.2)
			7	7	82.5 (15.6)	4.2 (12.0)	(-4.7, 13.0)
		22	.	1	73.7	3.0	
	2 - 22	1	.	6	79.4 (10.3)	-2.5 (8.5)	(-5.4, 0.3)
840 mg BID	1	1	2	3	76.9 (5.1)	0.7 (8.4)	(-13.4, 14.7)
			7	3	72.7 (5.4)	-3.6 (5.2)	(-12.3, 5.2)
		15	2	3	69.9 (5.7)	-6.3 (2.4)	(-10.4, -2.3)
			7	3	75.0 (6.5)	-1.2 (9.9)	(-17.8, 15.4)
		22	.	1	85.0	5.7	
	2 - 22	1	.	3	78.0 (8.6)	1.0 (7.4)	(-3.6, 5.6)

Table 11: Categorical Analysis for HR

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	55	50 (90.9%)	5 (9.1%)	55 (100%)	0 (0.0%)
40 - 500 mg QD	26	23 (88.5%)	3 (11.5%)	25 (96.2%)	1 (3.8%)
240 - 480 mg BID	20	17 (85.0%)	3 (15.0%)	19 (95.0%)	1 (5.0%)
600 mg BID	7	6 (85.7%)	1 (14.3%)	7 (100%)	0 (0.0%)
840 mg BID	3	3 (100%)	0 (0.0%)	3 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. No trend was observed for the effect of rucaparib on PR changes.

The outlier analysis results for PR are presented in Table 14.

**Table 12: Analysis Results of Δ PR for Food Effect Cohort
(Rucaparib 40 mg QD and 300 mg QD)**

				PR (ms)		Δ PR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
Food Effect Cohort	1	-7 (fasted)	2	9	164.1 (14.8)	0.3 (5.9)	(-3.3, 4.0)
			7	9	162.5 (16.4)	-1.3 (5.6)	(-4.7, 2.2)
		-1	.	9	160.9 (13.7)	-2.9 (5.4)	(-6.3, 0.5)
			2	9	155.7 (18.8)	-8.0 (9.7)	(-14.0, -2.0)
		1 (fed)	7	9	163.1 (15.6)	-0.6 (6.1)	(-4.4, 3.2)

Table 13: Analysis Results of Δ PR for Different Rucaparib Groups

				PR (ms)		Δ PR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
40 - 500 mg QD	1	1	2	17	151.5 (18.8)	9.1 (9.0)	(5.1, 13.0)
			7	16	148.9 (18.9)	4.6 (9.4)	(0.3, 8.9)
		15	2	23	159.2 (14.8)	5.9 (10.4)	(2.1, 9.7)
			7	23	156.2 (18.0)	2.9 (10.4)	(-0.9, 6.7)
		22	.	4	156.2 (14.5)	-7.1 (17.4)	(-27.6, 13.4)
			2 - 22	21	163.5 (16.7)	5.6 (12.3)	(3.9, 7.4)
240 - 480 mg BID	1	1	2	19	153.0 (22.9)	1.9 (5.7)	(-0.4, 4.2)
			7	20	151.8 (22.3)	0.0 (6.2)	(-2.4, 2.5)
		15	2	18	150.5 (24.1)	0.6 (5.9)	(-1.8, 3.0)
			7	18	150.0 (22.7)	0.1 (7.4)	(-2.9, 3.2)
		22	.	1	131.0	-7.7	
			2 - 22	17	155.8 (22.8)	0.9 (8.6)	(-0.6, 2.4)
600 mg BID	1	1	2	7	154.6 (33.9)	2.0 (8.7)	(-4.4, 8.4)
			7	7	155.8 (30.4)	3.2 (5.5)	(-0.8, 7.3)
		15	2	7	151.0 (25.9)	-1.5 (5.7)	(-5.7, 2.6)
			7	7	148.2 (25.9)	-4.3 (5.5)	(-8.4, -0.3)

				PR (ms)		ΔPR (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
		22	.	1	140.3	4.0	
	2 - 22	1	.	6	162.5 (31.2)	1.6 (7.7)	(-1.0, 4.2)
840 mg BID	1	1	2	3	149.0 (9.5)	-2.1 (4.7)	(-10.1, 5.9)
			7	3	155.3 (14.8)	4.2 (4.5)	(-3.4, 11.9)
		15	2	3	150.8 (11.4)	-0.3 (1.2)	(-2.4, 1.7)
			7	3	148.9 (9.1)	-2.2 (3.4)	(-7.9, 3.5)
		22	.	1	137.0	-4.7	
	2 - 22	1	.	3	145.6 (10.2)	-3.0 (4.7)	(-5.9, -0.1)

Table 14: Categorical Analysis for PR

Treatment Group	Total N		PR≤200 ms		PR>200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	55	55	54 (98.2%)	54 (98.2%)	1 (1.8%)	1 (1.8%)
40 - 500 mg QD	26	264	25 (96.2%)	262 (99.2%)	1 (3.8%)	2 (0.8%)
240 - 480 mg BID	20	168	17 (85.0%)	158 (94.0%)	3 (15.0%)	10 (6.0%)
600 mg BID	7	55	6 (85.7%)	49 (89.1%)	1 (14.3%)	6 (10.9%)
840 mg BID	3	22	3 (100%)	22 (100%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The magnitude of QRS changes was small and mostly non-significant in all rucaparib groups.

The outlier analysis results for QRS are presented in Table 17.

Table 15: Analysis Results of ΔPR for Food Effect Cohort (Rucaparib 40 mg QD and 300 mg QD)

				QRS (ms)		ΔQRS (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
Food Effect Cohort	1	-7 (fasted)	2	9	83.2 (5.6)	-0.9 (6.3)	(-4.8, 3.0)

				QRS (ms)		ΔQRS (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
			7	9	85.7 (6.9)	1.6 (8.0)	(-3.3, 6.6)
		-1	.	9	84.7 (7.1)	0.6 (4.7)	(-2.3, 3.5)
		1 (fed)	2	9	84.1 (9.6)	-0.0 (3.7)	(-2.3, 2.3)
			7	9	83.4 (5.7)	-0.7 (5.9)	(-4.4, 3.0)

Table 16: Analysis Results of ΔQRS for Different Rucaparib Groups

				QRS (ms)		ΔQRS (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
40 - 500 mg QD	1	1	2	17	87.9 (7.2)	0.9 (4.2)	(-1.0, 2.7)
			7	16	88.1 (6.9)	0.0 (3.2)	(-1.4, 1.4)
		15	2	23	86.6 (6.8)	0.9 (4.3)	(-0.7, 2.5)
			7	23	87.2 (7.4)	1.5 (3.7)	(0.2, 2.8)
		22	.	4	79.6 (10.2)	-1.1 (1.9)	(-3.3, 1.2)
	2 - 22	1	.	21	87.8 (6.4)	0.4 (4.2)	(-0.2, 1.0)
240 - 480 mg BID	1	1	2	19	91.3 (8.0)	1.8 (4.5)	(0.0, 3.6)
			7	20	90.5 (8.8)	1.0 (4.2)	(-0.6, 2.6)
		15	2	18	90.0 (9.4)	0.9 (4.6)	(-1.0, 2.7)
			7	18	89.1 (8.2)	-0.0 (5.4)	(-2.2, 2.2)
		22	.	1	85.0	-2.0	
	2 - 22	1	.	17	91.3 (8.5)	0.1 (4.9)	(-0.8, 0.9)
600 mg BID	1	1	2	7	89.7 (9.2)	1.9 (0.8)	(1.3, 2.5)
			7	7	89.8 (9.7)	2.0 (2.1)	(0.5, 3.5)
		15	2	7	87.5 (7.5)	-0.2 (3.5)	(-2.8, 2.3)
			7	7	88.2 (5.6)	0.5 (5.2)	(-3.3, 4.3)
		22	.	1	101.3	-2.3	
	2 - 22	1	.	6	88.3 (9.5)	0.6 (2.9)	(-0.4, 1.6)
840 mg BID	1	1	2	3	90.1 (10.3)	0.9 (1.6)	(-1.8, 3.5)

				QRS (ms)		Δ QRS (ms)	
Dose Group	Cycle	Day	Time (Hour)	N	Mean (SD)	Mean (SD)	90% CI
			7	3	90.0 (8.7)	0.8 (3.8)	(-5.6, 7.2)
		15	2	3	89.4 (15.6)	0.2 (5.4)	(-8.9, 9.4)
			7	3	89.6 (13.2)	0.3 (1.8)	(-2.6, 3.3)
		22	.	1	82.3	1.7	
	2 - 22	1	.	3	85.4 (9.6)	-1.4 (2.3)	(-2.8, 0.0)

Table 17: Categorical Analysis for QRS

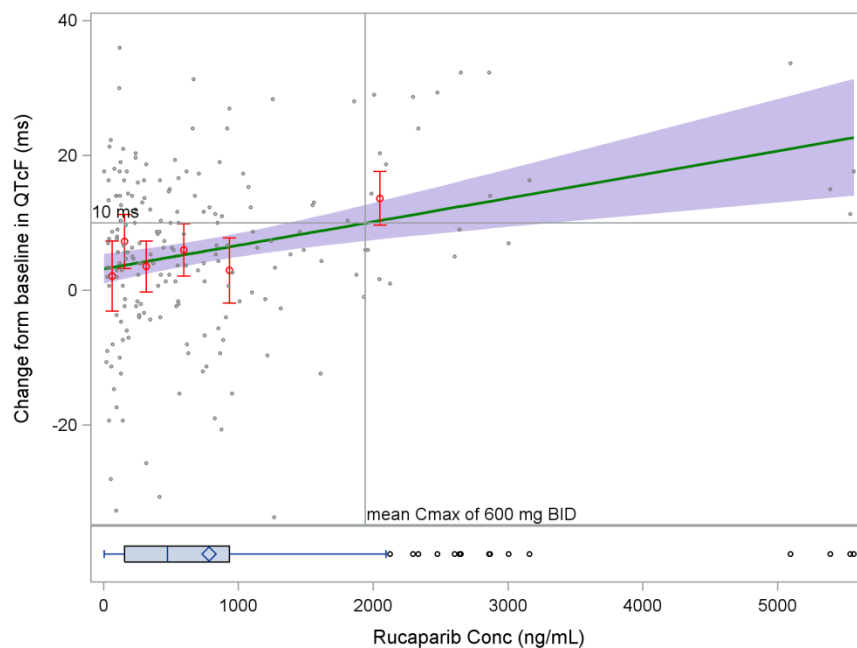
Treatment Group	Total N		QRS $\leq$ 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	55	55	55 (100%)	55 (100%)	0 (0.0%)	0 (0.0%)
40 - 500 mg QD	26	264	26 (100%)	264 (100%)	0 (0.0%)	0 (0.0%)
240 - 480 mg BID	20	168	19 (95.0%)	166 (98.8%)	1 (5.0%)	2 (1.2%)
600 mg BID	7	55	7 (100%)	55 (100%)	0 (0.0%)	0 (0.0%)
840 mg BID	3	22	3 (100%)	22 (100%)	0 (0.0%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1.

The linear mixed-effect model with intercept was able to fit the data better (based on the AIC value) compared to the log-linear model as proposed by the sponsor. According to the linear mixed-effect model, a significant relationship between Δ QTcF and rucaparib concentrations was observed (with a slope estimate of 3.9 ms/(μ g/ml), $p=0.02$). At the therapeutic steady state $C_{\max}$ of 1.94 μ g/ml (as provided in clinical pharmacology table based on the Part 3 PK data in Study CO-338-010) with the therapeutic dosing regimen of 600 mg BID, the mean Δ QTcF of 10.4 ms is estimated (Figure 5). At the observed mean $C_{\max}$ of 2.42 μ g/ml on day 15 (steady state $C_{\max}$) with the therapeutic dosing regimen of 600 mg BID, the mean Δ QTcF of 12.3 (with 90% CI: 7.6, 17) ms is estimated. At the mean $C_{\max}$ of 3.03 μ g/ml on day 15 (steady state $C_{\max}$) with the suprathreshold dosing regimen of 840 mg BID, the mean Δ QTcF of 14.7 (with 90% CI: 8.5, 20.8) ms is estimated.

Figure 5: Δ QTcF vs. Rucaparib Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

One subject in Part 1 experienced an SAE of atrial fibrillation.

There were 10 deaths in the study. Seven deaths were due to disease progression, 1 death was due to disease progression and hyponatremia, 1 death was due to pulmonary embolism, and 1 death was due to respiratory failure and disease progression (initially attributed to treatment-related dyspnea, but updated during a follow-up SAE report).

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	A rucaparib 600 mg twice daily (BID) given orally (PO) dose refers to free base rucaparib, formulated as rucaparib camsylate.				
	Mean (%CV) PK parameters after a single dose of 600 mg rucaparib:				
	Treatment	Meal Status	N	C _{max} (ng/mL)	AUC _{last} (ng·hr/mL)
	Single dose	Fasted	26	819 (84.2%)	10000 (75.7%) ^a
	Single dose	High-fat meal	26	959 (72.8%)	13900 (74.1%) ^a
	BID x 14 days	With or without food	18	1940 (54.2%)	15800 (57.6%) ^b
	^a PK sampling up to 24 hr post dose				
	^b PK sampling up to 10 hr post dose				
Maximum tolerated dose	MTD as defined in the Phase 1 dose-escalation portion of Study CO-338-010 (Study 10) was not reached. The highest rucaparib dose evaluated in Phase 1 was 840 mg BID; 600 mg BID rucaparib was selected as the Recommended Phase 2/3 Dose based on the overall safety, PK, and efficacy profile observed at that dose level.				
Principal adverse events	The most frequently reported (≥15% of patients) treatment-emergent adverse events (TEAEs) (all grades, all causality) in patients treated with 600 mg BID rucaparib (N=409) are:				
	Adverse Event			N=409 N (%)	
	Nausea			303 (74)	
	Asthenia/fatigue			299 (73)	
	Vomiting			178 (44)	
	Anemia/low/decreased hemoglobin			169 (41)	
	ALT/AST increased			162 (40)	
	Dysgeusia			151 (37)	
	Constipation			150 (37)	
	Decreased appetite			148 (36)	
	Diarrhea			126 (31)	
	Abdominal pain			119 (29)	
	dyspnea			83 (20)	
	Thrombocytopenia/low/decreased platelets			81 (20)	
	Blood creatinine increased			77 (19)	
	Abdominal distension			73 (18)	
	Headache			70 (17)	
	Dizziness			66 (16)	
	Neutropenia/low/decreased ANC			60 (15)	
Maximum dose tested	Single Dose		840 mg		
	Multiple Dose		840 mg BID		
Exposures Achieved at Maximum Tested Dose	Single Dose		C _{max} = 1380 ng/mL (CV = 69.4%, n=3) AUC ₀₋₁₀ = 9250 ng·hr/mL (CV = 69.6%, n = 3)		
	Multiple Dose		C _{max} = 3030 ng/mL (n = 2) AUC ₀₋₁₀ = 24900 ng·hr/mL (n=2)		
Range of linear PK	Approximate dose-linear PK at steady state following 40-500 mg daily (QD) and 240-840 mg BID as tested by linear regressions of log-transformed exposure and dose, i.e., Log(PK) = β ₀ + β ₁ ·Log(dose)				
	Dosing frequency	PK parameter	β ₁	90% confidence interval	R ²
	QD	C _{max}	0.92	0.69-1.15	0.79
		AUC ₀₋₂₄	0.98	0.72-1.25	0.78
	BID	C _{max}	1.03	0.42-1.63	0.26
		AUC ₀₋₁₀	1.04	0.42-1.67	0.25
Accumulation at steady state	The accumulation at steady state was determined using data from Study 10 Part 1. Accumulation ratio (40-500 mg QD) = 1.92 (CV = 34.5%, n = 15) Accumulation ratio (240-840 mg BID) = 3.88 (CV = 16.2%, n = 26)				

Metabolites	There are no metabolites standards synthesized and therefore, relative abundance of the parent molecule and proposed metabolites presented below were obtained using multiple reaction monitoring detection in an LC-MS/MS assay. In pooled plasma samples collected from 3 patients on cycle 1 day 15 at 600 mg BID in Study 10, rucaparib was the main circulating moiety, accounting for 50.5% of total peak area. Two metabolites, M324 (a carboxylate) and M338 (N-methylated carboxylate) were tentatively identified as major metabolites, accounting for 18.4% and 18.0% of total peak area, respectively. Metabolites M339a,b, M309, and M337c,d, each accounted for <9% of total peak area. Activity of the tentative metabolites was not determined. A definitive [¹⁴C]rucaparib ADME study in patients (CO-338-045) is planned.	
Absorption	Absolute/Relative Bioavailability	In Study A4991014 at doses of rucaparib 12 mg to 120 mg, the absolute bioavailability was dose-independent with a mean of 36% (CV = 38%, n = 31).
	T _{max}	In Study 10 Part 3 (oral dosing at 600 mg BID), steady state rucaparib T _{max} = 1.92 hr (range = 0 to 5.98; n = 18). T _{max} for the identified metabolites was not determined.
Distribution	V _d /F or V _d	In Study A4991014 following a single IV dose at 12 to 40 mg, V _{ss} = 251 L (CV = 49.8%, n = 33)
	% bound	70.2%
Elimination	Route	To be evaluated in Study CO-338-045
	Terminal t _{1/2}	In Study 10 Part 3 following a single oral dose at 600 mg: - Fasted: T_{1/2} = 18.7 hr (CV = 52.7%, n = 19) - High-fat meal: T_{1/2} = 16.8 hr (CV = 56.5%, n = 11) In Study A4991014 following a single IV doses at 12 mg to 40 mg: - T_{1/2} = 17.6 hr (CV=30.8%, n = 34) T _{1/2} of metabolites were not determined.
	CL/F or CL	In Study A4991014 following a single IV dose at 12 mg to 40 mg, CL = 17.7 L/hr (CV = 50.3%, n = 33)
Intrinsic Factors	Age	Being evaluated as part of PPK analysis
	Sex	Inconclusive due to low number of male subjects.
	Race	Being evaluated as part of PPK analysis
	Hepatic & Renal Impairment	Being evaluated as part of PPK analysis
Extrinsic Factors	Drug interactions	A (b)(4) DDI study in patients (CO-338-044) has initiated to assess DDI with rucaparib as a perpetrator of CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp. PPK analysis is ongoing to assess effect of genotypes of CYP1A2 and CYP2D6 (using data from Study CO-338-017 [ARIEL2]) and concomitant medicines on rucaparib PK (using data from ARIEL2 and Study 10).

	Food Effects	In Study 10 Part 3, rucaparib PK following a single dose at 600 mg under fasted condition or with a high-fat meal was determined (n=26).				
		Parameter	LS GeoMean		Ratio (%)	90% CI
			Fed	Fasted	Fed/fasted	
		C _{max} (ng/mL)	757	630	120	99.1-146
		AUC ₀₋₂₄ (ng·hr/mL)	10900	7920	138	117-162
Expected High Clinical Exposure Scenario	The highest tested dosage was 840 mg BID, and the RP2D and proposed labeled dosage is 600 mg BID. No supra-therapeutic dose above 840 mg BID was tested.					
Preclinical Cardiac Safety	In a GLP in vitro assay for hERG activity, the IC₅₀ for the inhibitory effects of rucaparib on hERG potassium currents was 22.6µM, which is 13-fold higher than the mean unbound plasma C_{max} (1.79µM) observed in patients treated with 600 mg BID rucaparib. A GLP safety pharmacology cardiovascular (CV) study in conscious telemetry-instrumented dogs given rucaparib IV up to 15 mg/kg was conducted. No adverse cardiovascular effects were noted at 15 mg/kg. This dose corresponded to a C_{max} of 2542 ng/mL that is 1.3-fold higher than the total plasma C_{max} of 1940 ng/mL measured in patients treated with 600 mg BID rucaparib. Additional CV monitoring was conducted in GLP repeat-dose studies in dog given rucaparib PO. No ECG changes were observed at doses up to 75 mg/kg/day (30-day repeat-dose study) and 20 mg/kg/day (91-day repeat-dose study) as well as no alterations in hemodynamic parameters or vital signs noted in the 91-day study. At 75 mg/kg, the C_{max} was 1680 and 2460 ng/mL for male and female dogs, respectively, which was approximately equivalent to the C_{max} of 1940 ng/mL in patients treated with 600 mg BID of rucaparib. Conversely, cardiac effects were observed in rats and dogs following IV, but not oral dosing, of rucaparib. In the rat, pathologic changes in the heart were described as myocardial degeneration, necrosis and fibroplasia at 75 mg/kg/day in a 5-day study. The mean C_{max} at this dose was 10538 ng/mL which is approximately 5-fold above the C_{max} of 1940 ng/mL in patients treated with 600 mg BID of rucaparib. In the dog, ECG abnormalities described as persistent sinus tachycardia, atrioventricular nodal rhythm were recorded at 40 mg/kg/day for 5 days as well as a higher incidence of endocardial hemorrhage at that dose. This dose corresponded to mean C_{max} of 14245 ng/mL which is approximately 7-fold higher than the C_{max} of 1940 ng/mL in patients treated with 600 mg BID of rucaparib. Exposure data from IV and PO studies in rat and dog indicate that the C_{max} values were much higher in the IV studies as compared to the PO studies. Furthermore, the C_{max} values in the IV studies that reported microscopic cardiac changes were higher than the C_{max} values reported in IV studies without cardiac changes. In contrast, the AUC values were slightly higher or approximately equivalent when given PO, in rat and dog, respectively, than what was measured in the IV study where cardiac lesions were noted. These data indicate that the development of cardiac lesions in rats and dogs following IV dosing of rucaparib appears to be C_{max} driven. Thus, when given PO, rucaparib poses a low risk for causing cardiac lesions in patients.					

Clinical Cardiac Safety	The Phase 1 (Part 1) dose-escalation portion of Study 10 included serial ECGs (as triplicate reads) and independent central review in order to assess the effect of oral rucaparib on QTc. The primary endpoint for analyses of QTc was change from Baseline (Day -1 prior to Cycle 1) in QTcF (ΔQTcF). The secondary endpoint for analyses of QTc was change from Baseline in QTcB (ΔQTcB). A total of 55 patients treated at rucaparib doses ranging from 40 mg QD to 840 mg BID had data available for analysis of change from Baseline. At the time of the analysis, ECG data was available for up to 22 cycles in the patient with the longest duration on treatment. A summary of the findings include: • No patient had a QTc >500 msec • Only 1 patient had a QTcF $\geq$480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation that was not prohibited per protocol. This patient continued to receive monotherapy rucaparib at a dose of 480 mg BID with no further QTcF measurement $\geq$480 msec. • Only 1 patient had a QTc increase from baseline >60 msec. This patient had a history of QT prolongation prior to study entry and received 1 dose of rucaparib before discontinuing from the study due to eligibility violation. • Rucaparib in doses up to 840 mg BID exhibited a mean change of QTcF from Baseline of 11.3 msec at the maximum concentration (5565 ng/mL) observed in the study; the alteration of the mechanism of repolarization was minimal. • At a dose of 600 mg BID, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec • Outlier values of QTc and change of QTc, as well as emergent morphology findings, were minimal. • T wave morphology changes were present in only a small number of cases • HR, PR, QRS and morphology findings were normal The overall assessment by central review was that the magnitude of the QTc increase was small and the alteration of the mechanism of repolarization was minimal within the myocardium. In addition, the magnitude of the effect is likely to be of no consequence for predicting cardiac arrhythmia liability. The following TEAEs (preferred term, all grades, all causality) in the Cardiac Disorders System Organ Class have been reported in patients treated with 600 mg BID rucaparib (N=409) in open-label Clovis-sponsored clinical studies: angina pectoris (n=1, 0.2%), atrial fibrillation (n=1, 0.2%), atrial tachycardia (n=1, 0.2%), cardiac failure (n=1, 0.2%), myocardial ischemia (n=1, 0.2%), palpitations (n=11, 2.7%), pericardial effusion (n=1, 0.2%), sinus tachycardia (n=1, 0.2%), and tachycardia (n=3, 0.7%). In addition, the following related TEAEs were reported in other System Organ Classes: long QT syndrome congenital (n=1, 0.2%), chest discomfort (n=4, 1.0%), chest pain (n=4, 1.0%), non-cardiac chest pain (n=10, 2.4%), cardiac murmur (n=1, 0.2%), electrocardiogram QT prolonged (n=3, 0.7%), electrocardiogram low voltage (n=1, 0.2%), heart rate irregular (n=1, 0.2%), troponin I increased (n=1, 0.2%), Troponin T increased (n=1, 0.2%), presyncope (n=7, 1.7%), syncope (n=6, 1.5%), and coronary arterial stent insertion (n=1, 0.2%). No sudden deaths have been reported in rucaparib-treated patients.
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/s/

JIANG LIU
10/06/2016

QIANYU DANG
10/07/2016
Janell Chen was the primary stats reviewer

CHRISTINE E GARNETT
10/07/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 29, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 209115
Product Name and Strength:	Rubraca (rucaparib) Tablets, 200 mg and 300 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Clovis Oncology Inc.
Submission Date:	June 23, 2016 and September 15, 2016
OSE RCM #:	2016-1050
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Clovis Oncology Inc. submitted Rubraca (rucaparib) container labels and prescribing information (PI) for NDA 209115. The Division of Oncology Products 1 (DOP1) requested that we review the submitted Rubraca container labels and PI for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluate the proposed Rubraca container labels and determine that the container labels can be improved by removing (b) (4) in the strength statement to minimize information crowding.

The proposed PI is acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels for Rubraca may be improved to promote the safe use of the product as described in Section 4.1. However, the proposed PI is acceptable from a medication error perspective, and we have no further recommendations for the proposed PI at this time.

4.1 RECOMMENDATIONS FOR CLOVIS ONCOLOGY INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container labels

1. Remove (b) (4) from the strength statement “#00 mg* (b) (4)” to reduce information crowding on the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rubraca that Clovis Oncology Inc. submitted on June 23, 2016.

Table 2. Relevant Product Information for Rubraca											
Initial Approval Date	N/A										
Active Ingredient	rucaparib										
Indication	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.										
Route of Administration	Oral										
Dosage Form	Tablets										
Strength	200 mg, 300 mg										
Dose and Frequency	600 mg orally twice daily To manage adverse reactions, consider interruption of treatment or dose reduction. Recommended dose reductions are indicated below: <table> <tr> <th>Dose Reduction</th><th>Dose</th></tr> <tr> <td>Starting Dose</td><td>600 mg twice daily (two 300 mg tablets)</td></tr> <tr> <td>First Dose Reduction</td><td>500 mg twice daily (one 300 mg tablet and one 200 mg tablet)</td></tr> <tr> <td>Second Dose Reduction</td><td>400 mg twice daily (two 200 mg tablets)</td></tr> <tr> <td>Third Dose Reduction</td><td>300 mg twice daily (one 300 mg tablet)</td></tr> </table>	Dose Reduction	Dose	Starting Dose	600 mg twice daily (two 300 mg tablets)	First Dose Reduction	500 mg twice daily (one 300 mg tablet and one 200 mg tablet)	Second Dose Reduction	400 mg twice daily (two 200 mg tablets)	Third Dose Reduction	300 mg twice daily (one 300 mg tablet)
Dose Reduction	Dose										
Starting Dose	600 mg twice daily (two 300 mg tablets)										
First Dose Reduction	500 mg twice daily (one 300 mg tablet and one 200 mg tablet)										
Second Dose Reduction	400 mg twice daily (two 200 mg tablets)										
Third Dose Reduction	300 mg twice daily (one 300 mg tablet)										
How Supplied	200 mg and 300 mg: Bottle of 60 tablets										
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].										
Container Closure	(b) (4)										

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TINGTING N GAO
09/29/2016

CHI-MING TU
09/29/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209115

Application Type: New NDA

Drug Name(s)/Dosage Form(s): RUBRACA™ (rucaparib camsylate) Tablets; 200 mg and 300 mg

Applicant: Clovis Oncology, Inc.

Receipt Date: June 23, 2016

Goal Date: December 23, 2016

1. Regulatory History and Applicant's Main Proposals

- September 25, 2009, IND 106289 was deemed safe to proceed by the FDA
- July 31, 2012, Orphan Designation was granted
- November 4, 2014, an EOP2 Meeting was held to discuss Study CO-338-010 (Phase 1/2) and Study CO 338-017 (Phase 2) and the clinically meaningful advantage of rucaparib over existing therapies
- April 13, 2015, Breakthrough Therapy Designation was granted
- April 14, 2016, a Type B, Pre NDA Content & Format meeting was held to discuss the proposed content and format of the planned NDA

Clovis Oncology, Inc. submitted a New Drug Application (NDA) on June 23, 2016, for the use of rucaparib as monotherapy treatment for patients with advanced ovarian cancer, in patients with deleterious BRCA-mutated tumors, inclusive of both germline and somatic BRCA mutations as detected by an FDA approved test. This submission was submitted as a Rolling Review.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

In addition, the following labeling issues were identified:

1. Highlights: The name of drug product should appear in UPPER CASE letters.

Selected Requirements of Prescribing Information

2. Full Prescribing Information, Adverse Reactions section, Clinical Trials Experience subsection: In the introductory paragraph, “Because clinical (b) (4) are conducted under widely varying conditions....”, the word (b) (4) should be changed to “trials” in two places.
3. Highlights, Indications and Usage: Add a “(1)” behind the following statement:
Rubraca is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy
(b) (4)

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the Applicant in the 74-day letter/an advice letter. The Applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 16, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES

Selected Requirements of Prescribing Information

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment: *The drug name product does not appear in UPPER CASE letters.*

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment: *There is no Boxed Warning for this drug.*

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *There is no RMC changes, as this is USPI is the first of its kind.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *The product only has one dosage form.*

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: The word ^{(b) (4)} should be changed to “trials”.

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

KIM J ROBERTSON
08/31/2016

CHRISTY L COTTRELL
09/01/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209115	NDA Supplement #: S- N/A	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (TBD) Established/Proper Name: rucaparib camsylate Dosage Form: tablet Strengths: 200 mg & 300 mg		
Applicant: Clovis Oncology, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: June 23, 2016 Date of Receipt: June 23, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: February 23, 2017		Action Goal Date (if different): December 16, 2016
Filing Date: August 22, 2016		Date of Filing Meeting: August 12, 2016
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline and somatic BRCA mutations as detected by an FDA approved test.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment”</i>		

<i>review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .	
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Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: <i>The application will be a priority review if:</i> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☐ Standard ☒ Priority (Expedited) ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☒ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: N/A	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): #106289				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	☒	☐		

<i>to the supporting IND(s) if not already entered into electronic archive.</i>					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.				X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐	X	
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		Application was granted Orphan Designation 7/31/2012
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>		☐	☐	X	

cover letter, and annotated labeling). If yes , answer the bulleted questions below:																					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☐																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☐																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		☐	☐																		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>																					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☐																		
If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
Exclusivity	YES	NO	NA	Comment																	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒																			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐																		
If yes, # years requested: 5 years																					
<i>Note: An applicant can receive exclusivity without requesting it;</i>																					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes , BLA # N/A				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☐	☒		Will request form in the 74-day letter
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☒	☐	This application was granted Orphan Designation and is therefore exempt from pediatric studies requirements
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	DMPP Consulted: 6/30/2016; CDRH: 7/1/2016
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 4, 2014	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 4, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s): N/A	☐	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 12, 2016

BACKGROUND: Clovis Oncology, Inc. submitted a rolling review submission for its NDA 209115 for rucaparib camsylate as a monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline and somatic BRCA mutations as detected by an FDA approved test.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim J. Robertson	Y
	CPMS/TL:	Christy Cottrell	N
Cross-Discipline Team Leader (CDTL)	Julia Beaver, MD		Y
Division Director/Deputy	Geoffrey Kim, MD		Y
Office Director/Deputy	Richard Pazdur, MD		N
Clinical	Reviewer:	Sanjeeve Balasubramaniam, MD Sara Horton, MD	Y
	TL:	Julia Beaver, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Jinzhong Liu, PharmD; Sarah Schrieber, PharmD	
	TL:	Pengfei Song, PhD	
• Genomics	Reviewer:	Robert (Bob) Schuck, PhD	
• Pharmacometrics	Reviewer:	Chao Liu, PharmD	

		TL: Jingyu (Jerry) Yu, PhD	
Biostatistics	Reviewer:	Laura Fernandes, PhD	
	TL:	Shenghui Tang, PhD	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Haw-Jyh (Brian) Chiu, PhD	
	TL:	Todd Palmby, PhD	
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Product Quality (CMC) Review Team:	ATL:	Xiao-Hong Chen, PhD	
	RBPM:	Kristine Leahy, RPh	
• Drug Substance	Reviewer:	Monica Cooper, PhD	
• Drug Product	Reviewer:	Xing Wang, PhD	
• Process	Reviewer:	Daniel Obrzut, PhD	
• Microbiology	Reviewer:	Daniel Obrzut, PhD	
• Facility	Reviewer:	Ruth Moore, PhD	
• Biopharmaceutics	Reviewer:	Jing Li, PhD; TL: Okpo Eradiri, PhD	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Raanan Bloom, PhD (EA Reviewer) Kasturi Srinivasachar; DS/DP TL Anamitro Banerjee, PhD; Branch Chief		
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina, PharmD	
	TL:	Barbara Fuller, PharmD	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Nicholas Senior, PharmD	
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao, PharmD	
	TL:	Chi-Ming (Alice) Tu, PharmD	
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen; PharmD	
	TL:	Naomi Redd, PharmD	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor, PhD	
	TL:	Susan Thompson, MD	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines			
Discipline	Reviewer:	CDRH Reviewer= Hisani Madison, PhD CDRH Branch Chief= Reena Philip, PhD CDRH Director= Eunice Lee, PhD	
	TL:		
Other attendees	ERG Assessor:	(b) (6)	

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain	☒ YES ☐ NO	
Electronic Submission comments	☐ Not Applicable	

List comments:	☒ No comments
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CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: the application did not raise significant safety or efficacy issues.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☐ YES ☒ NO
• What late submission components, if any, arrived after 30 days?	On Day 34, the dissolution method development report and 12-month long-term stability data.
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): October 20, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

KIM J ROBERTSON
08/19/2016

CHRISTY L COTTRELL
08/22/2016