

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208447Orig1s000**

**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.

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NDA # 208447  
Product Name: Zejula™ (niraparib)

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PMR Description: 3187-1  
Conduct a dedicated pharmacokinetic trial in patients with moderate hepatic impairment to determine an appropriate starting dose of niraparib in patients with moderate hepatic impairment.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>06/2017</u>
	Trial Completion:	<u>11/2018</u>
	Final Study Report Submission:	<u>02/2019</u>

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. For safety concerns, these patients were excluded from the clinical trials. 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 objective of this trial is to determine the appropriate starting dose for patients with moderate hepatic impairment.

The PK and safety data of niraparib in patients with moderate hepatic impairment are unknown, as only two patients were categorized as having moderate or severe hepatic impairment. As niraparib is predominantly metabolized by carboxylesterase, patients with moderate hepatic impairment may have compromised carboxylesterase activity, which may potentially lead to increased exposure of niraparib and subsequently serious adverse events.

A dedicated study examining the PK and safety of niraparib in a group of patients with moderate hepatic impairment will be useful to determine the magnitude of exposure changes and estimate the appropriate starting dose for 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.

The trial should be an open-label, non-randomized, phase 1 design of a single oral dose of 300 mg niraparib in sufficient number of patients with healthy liver and moderate hepatic impairment. The PK parameters along with safety data will be used to determine the appropriate starting dose for this patient subpopulation.

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

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**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)

## 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.

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NDA # 208447  
Product Name: Zejula™ (niraparib)

---

PMC Description: 3187-2  
Submit to FDA the appropriate analytical and clinical validation study for the in vitro diagnostic assay used to identify patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer with homologous recombination deficiency (HRD) in clinical trial entitled “A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer” to inform product labeling for both the device and for Niraparib.

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PMC Schedule Milestones: Final Report Submission: 12/2017

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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

In the non-gBRCAmut Cohort in the NOVA clinical trial, an improved progression free survival is seen in HRD-positive patients. An approved device should be available to assist practitioners in determining the expected benefit in their patient and thus, the risk-benefit profile of niraparib in the individual patient.

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.”

Not a PMR

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.

Data from the existing clinical trial NOVA, along with information concerning assay reproducibility, accuracy, etc. in patients with ovarian cancer could be submitted to fulfill this PMC.

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  
Conduct an assay validation study for HRD status in patients with ovarian cancer
- 

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

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**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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(signature line for BLAs)

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/ Product Name: 208447  
Zejula™ (niraparib)

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PMC Description: 3187-3  
Revise as necessary in-coming material quality controls and/or formulation and/or unit operation(s) such that the current practice of releasing drug product [REDACTED] (b) (4) while still maintaining product quality and batch to batch consistency.

---

PMC Schedule Milestones:

Final Report Submission: 04/2018

**Study rationale:** The applicant's current manufacturing process involves releasing drug product [REDACTED] (b) (4)

The quality and batch to batch consistency of your drug product should be based on sound understanding of the science and well designed and controlled manufacturing process, instead of on testing.

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
  - **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
  - **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**
1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.
- Need for drug (unmet need/life-threatening condition)
  - Long-term data needed (e.g., stability data)
  - Only feasible to conduct post-approval
  - Improvements to methods
  - Theoretical concern
  - Manufacturing process analysis
  - Other

The NDA was reviewed in a priority review clock. The identified deficiency is related to the drug product manufacturing process. Addressing the deficiency requires that the applicant perform additional studies and optimizing the process followed by validation, which cannot be fulfilled in the current review cycle.

2. Describe the particular review issue and the goal of the study.

The current manufacturing process involves releasing drug product (b) (4)

The quality and batch to batch consistency of your drug product should be based on sound understanding of the science and well designed and controlled manufacturing process, instead of on testing. Post Marketing Commitment will assure that firm conducts further investigation of the manufacturing process, improve/revise and validate the manufacturing process. The improvement/revision may include but not limited to, for example, in-coming material quality controls, formulation, unit operation(s); in-process controls whichever is necessary.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?

- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**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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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/ Product Name: 208447  
Zejula™ (niraparib)

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PMC Description: 3187-4 Provide method validation data for accuracy and precision using revised dissolution method AM-1974 and capsules made by the manufacturing process approved in the application. Data should be presented in the form of drug release profiles collected at 5, 15, 30, 45 and 60 minutes. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

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PMC Schedule Milestones:

Final Report Submission:

04/2018

**Study rationale:** The applicant's current method validation study fails to meet the acceptance criteria for accuracy and precision due to interference from the drug product. The applicant has committed to submit the requested study after the application is approved and after the method description has been updated with method description information accepted in the NDA.

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The NDA was reviewed in a priority review clock. The identified deficiency is related to the regulatory drug product specification for dissolution. Addressing the deficiency requires that the applicant perform an additional study which meets the expectations of the ICH Q2 guideline.

2. Describe the particular review issue and the goal of the study.

To establish that the regulatory method for dissolution is valid for accuracy and precision as described under the ICH Q2 guideline. The applicant has committed to submit a supplemental application within 30 days of NDA approval for updating the method description with information accepted in the NDA, then will provide the completed method validation study.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The applicant will provide a completed validation study which establishes that the method meets the ICH Q2 expectations for accuracy and precision.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**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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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/ 208447  
Product Name: Zejula™ (niraparib)

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PMC Description: 3187-5 Provide method validation data for accuracy and precision using the revised assay method AM-1971 and capsules made by the manufacturing process approved in the application. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

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PMC Schedule Milestones:

Final Report Submission:

04/2018

**Study rationale:** The applicant's current method validation study fails to meet the acceptance criteria for accuracy and precision due to interference. Applicant has committed to submit the requested study after the application is approved and after the method description has been updated with information accepted in the NDA.

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The NDA was reviewed in a priority review clock. The identified deficiency is related to the regulatory drug product specification for assay and related substances. Addressing the deficiency requires that the applicant perform an additional study which meets the expectations of the ICH Q2 guideline.

2. Describe the particular review issue and the goal of the study.

To establish that the regulatory method for assay is valid for accuracy and precision as described under the ICH Q2 guideline. The applicant has committed to submit a supplemental application within 30 days of NDA approval for updating the method description with information accepted in the NDA, then will provide the completed method validation study.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The applicant will provide a completed validation study which establishes that the method meets the ICH Q2 expectations for accuracy and precision.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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**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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(signature line for BLAs only)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINA D MARSHALL  
03/23/2017

KATHERINE M FEDENKO  
03/23/2017



## Consult Memorandum

**Date:** March 16, 2017

**To:** Gwynn Ison, M.D., Clinical Reviewer, CDER/OND/OHOP/DOP1  
Jeanette Dinin, RPM, CDER/OND/OHOP/DOP1

**From:** Soma Ghosh, Ph.D., Scientific Reviewer, CDRH/OIR/DMGP/MPCB Soma Ghosh -S  
2017.03.16 11:50:36 -04'00'  
Hisani Madison, Ph.D., M.P.H., Scientific Reviewer, CDRH/OIR/DMGP/MPCB Hisani N. Horne -S (Affiliate)  
2017.03.16 12:19:18 -04'00'

**Through:** Eunice Lee, Ph.D., Branch Chief, CDRH/OIR/DMGP/MPCB  
Reena Philip, Ph.D., Division Director, CDRH/OIR/DMGP

**Subject:** CDRH consult for NDA 208447

**PMA #:** P140020/S009 PMA supplement for BRACAnalysis CDx™ and

(b) (4)

**Drug Sponsor:** Tesaro, Inc.

**Drug Name:** Zejula™ (niraparib)

### BACKGROUND

Tesaro, Inc. (Tesaro), the sponsor for NDA 208447, is seeking full approval of niraparib, from CDER, for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a complete or partial response to platinum-based chemotherapy based on the results of the NOVA clinical study (PR-30-5011-C). Enrollment into the cohorts of the NOVA study was determined by the results of Myriad's Integrated BRACAnalysis testing and/or myChoice® HRD testing. Prior to randomization, a blood sample from each patient was tested for germline BRCA mutation using the BRACAnalysis CDx test. If the patient was negative for a germline BRCA mutation, the patient was enrolled in the non-gBRCAmut cohort and their tumor tissue tested using the myChoice HRD CDx test.

Myriad Genetic Laboratories, Inc. (Myriad) submitted a PMA supplement (P140020/S009) for the BRACAnalysis CDx on December 20, 2016 to request a new indication for the BRACAnalysis CDx test. (b) (4)

contemporaneous approvals of (b) (4) products. During review of NDA 208847, CDER designated (b) (4) the tests as complementary diagnostics.

(b) (4)

Tesaro, Inc. agreed to a postmarket commitment to provide the appropriate analytical and clinical validation data for the myChoice HRD CDx to inform product labeling for both the therapeutic and the device. Please refer to PMC #4 dated March 6, 2017.

#### **BRACAnalysis CDx Review Summary:**

Original PMA P140020 for the BRACAnalysis CDx test was approved by FDA in 2014 as a companion diagnostic for use with Lynparza (olaparib). On December 20, 2016, Myriad submitted a PMA supplement (P140020/S009) for the BRACAnalysis CDx to expand its intended use statement to include niraparib. The PMA supplement review for BRACAnalysis CDx has been completed and is summarized in this memo.

#### **INTENDED USE (BRACAnalysis CDx™)**

BRACAnalysis CDx is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR.

Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants, who are or may become eligible for treatment with Lynparza™ (olaparib). Detection of deleterious or suspected deleterious germline BRCA variants by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression free survival (PFS) from Zejula® (niraparib) maintenance therapy. This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

#### **INDICATION (Zejula™)**

Zejula™ is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

#### **REVIEW SUMMARY**

*NOVA Clinical Study (PR-30-5011-C)*

##### *Study Objectives*

The primary study objective was to evaluate the efficacy of niraparib as maintenance treatment of patients with platinum-sensitive, recurrent ovarian cancer who were in response to platinum-based chemotherapy, as assessed by the prolongation of progression-free survival (PFS). The objective was independently evaluated in a cohort of patients with germline breast cancer susceptibility gene (BRCA) mutation tumors (gBRCAmut cohort) and in a cohort of patients with high-grade serous or high-grade

predominantly serous histology, but who were not gBRCAmut carriers (non-gBRCAmut cohort). The statistical analysis of the primary endpoint of PFS for the non-gBRCAmut cohort was performed in a hierarchical manner, with a test for the group of patients with homologous recombination deficiency-positive (HRDpos) tumors performed first, followed by a test of the overall non-gBRCAmut cohort, if the first test was statistically significant.

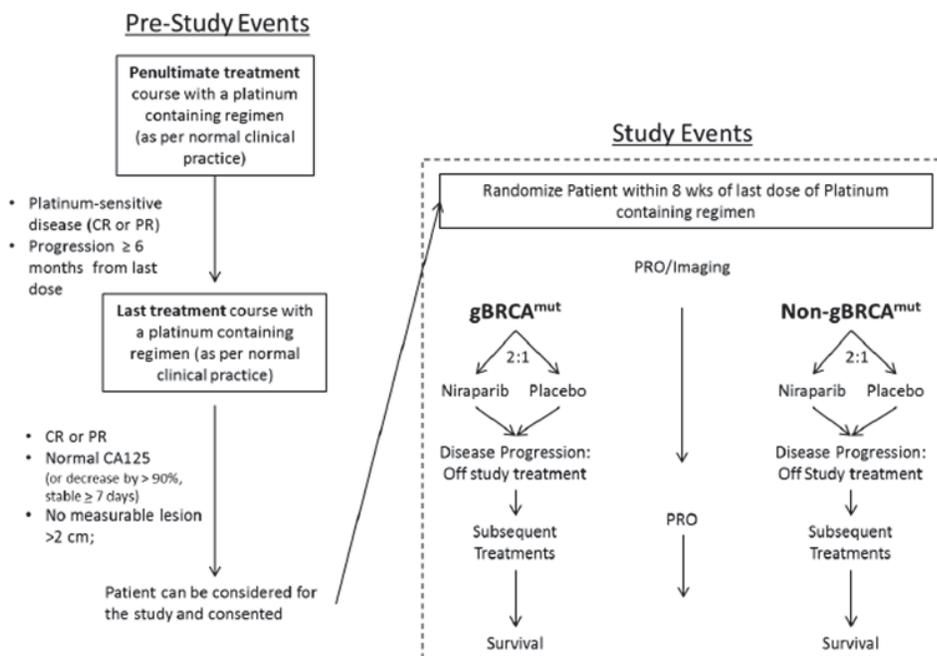
Secondary objectives of the main study included the following:

- To evaluate additional measures of clinical benefit, including patient-reported outcomes (PROs), time to first subsequent treatment (TFST), chemotherapy-free interval (CFI), progression-free survival 2 (PFS2), time to second subsequent treatment (TSST), and overall survival (OS).
- To evaluate the safety and tolerability of niraparib compared to placebo in the indicated target population.

*Study Methodology*

Study PR-30-5011-C is a double-blind, 2:1 (niraparib:placebo) randomized, placebo-controlled evaluation of patients with platinum-sensitive, recurrent ovarian cancer who had either germline BRCA mutation or a tumor with high-grade serous or high-grade predominantly serous histology without a germline BRCA mutation (non-gBRCAmut), who were in response to their last platinum-based therapy. Enrollment into the cohorts (as shown in the study scheme below) was determined by the results of Myriad’s Integrated BRCAAnalysis® test. Randomization was stratified by time to progression after the penultimate platinum therapy before study enrollment (6 to <12 months or ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no); and best response during the last platinum regimen (complete response [CR] or partial response [PR]). Tumor tissue samples were obtained and evaluated with the myChoice® HRD test for patients without germline mutation.

**Ovarian Maintenance Study Design**



### NOVA Study Efficacy Results

As outlined in the table below, niraparib met the primary efficacy endpoint of prolonging PFS versus placebo in all 3 prospectively defined primary patient populations (gBRCAmut cohort, HRDpos group of the non gBRCAmut cohort, and the overall non gBRCAmut cohort), and the treatment effect was statistically significant and consistent for all 3 primary efficacy populations. Thus, the treatment effect for niraparib was observed in all platinum-sensitive, recurrent ovarian cancer patients, although there were differential outcomes associated with biomarker status.

**Table 1. Efficacy Results**

Treatment	Median PFS <sup>a</sup> (95% CI) (Months)	Hazard Ratio <sup>b</sup> (95% CI) p-value <sup>c</sup>	% of Patients without Progression or Death at <sup>d</sup> :		
			6 Months	12 Months	18 Months
<b>gBRCAmut Cohort</b>					
Niraparib (N=138)	21.0 (12.9, NE)	0.27 (0.173, 0.410) p<0.0001	80%	62%	50%
Placebo (N=65)	5.5 (3.8, 7.2)		43%	16%	16%
<b>HRDpos Group</b>					
Niraparib (N=106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586) p<0.0001	69%	51%	37%
Placebo (N=56)	3.8 (3.5, 5.7)		35%	13%	9%
<b>Non-gBRCAmut Cohort</b>					
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	61%	41%	30%
Placebo (N=116)	3.9 (3.7, 5.5)		36%	14%	12%

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; gBRCAmut=germline BRCA mutation; HRDpos=homologous recombination deficiency positive; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation; PFS=progression-free survival

<sup>a</sup> Progression-free survival is defined as the time in months from the date of randomization to progression or death.

<sup>b</sup> Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.

<sup>c</sup> Based on stratified log-rank test using randomization stratification factors.

<sup>d</sup> Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

Upon careful review of the primary efficacy results, it appears that the observed results (see Table 2 below) are largely driven by germline (gBRCAmut cohort) and somatic BRCA mutation carriers (somatic BRCAmut, a subgroup of the HRD positive cohort) as the efficacy margin in the HRD-BRCAwt subgroup is minimal. At the mid-cycle NDA 208447 meeting, CDER stated that they consider the BRCAAnalysis CDx (and the myChoice HRD test) as a complementary diagnostic test for niraparib maintenance treatment in ovarian cancer patients since the efficacy margins of both the marker-positive (gBRCAmut cohort) and marker-negative (non-gBRCAmut cohort) cohorts are statistically significant.

**Table 2\***

	Treatment	Median PFS (95% CI) (Months)	Hazard Ratio (95% CI) p-value
<b>gBRCA mut Cohort</b> (BRACAnalysis CDx)	Niraparib (N=139)	21.0 (12.9, NE)	0.27 (0.173, 0.410)
	Placebo (N=65)	5.5 (3.8, 7.2)	p<0.0001
<b>non-gBRCAmut Cohort</b> (myChoice HRD CDx)	Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607)
	Placebo (N=116)	3.9 (3.7, 5.5)	p<0.0001
HRD Positive	Niraparib (N=106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586)
	Placebo (N=56)	3.8 (3.5, 5.7)	p<0.0001
<i>somatic BRCAmut</i>	Niraparib (N=35)	20.9 (9.7, NE)	0.27 (0.081, 0.903)
	Placebo (N=12)	11.0 (2.0, NE)	p=0.0248
<i>BRCAwt</i>	Niraparib (N=71)	9.3 (5.8, 15.4)	0.38 (0.231, 0.628)
	Placebo (N=44)	3.7 (3.3, 5.6)	p=0.0001
HRD Negative	Niraparib (N=92)	6.9 (5.6, 9.6)	0.58 (0.361, 0.922)
	Placebo (N=42)	3.8 (3.7, 5.6)	p=0.0226

\*The table was presented at the CDER mid-cycle NDA 208447 meeting.

#### *Clinical Performance of the BRACAnalysis CDx test – Bridging Study*

Since Myriad's Integrated BRACAnalysis test was used to select patients for enrollment into the NOVA study, a bridging study was conducted to support the clinical performance of Myriad's BRACAnalysis CDx test (final CDx). Among the 553 patients enrolled in the study, 532 had samples with sufficient residual material for testing with the BRACAnalysis CDx device. Eight (8) samples were excluded due to incomplete or partial testing or lack of sufficient sample quality. A total of 524 samples had valid results by both assays and there was 100% concordance for all calls. Further, the clinical outcome associated with the Integrated BRACAnalysis test results was maintained when the primary efficacy endpoint was calculated using the 524 patients tested by the BRACAnalysis CDx test. The results are in the table below.

**Table 3. Bridging Study Results based on the BRACAnalysis CDx**

Parameter	Non-gBRCAmut Overall		gBRCAmut	
	Niraparib (n=221)	Placebo (n=109)	Niraparib (n=130)	Placebo (n=64)
<b>Median PFS (95% CI) months</b>	9.3 (7.2, 11.3)	3.9 (3.7, 5.6)	21.2 (12.7, NE)	5.5 (3.8, 7.2)
<b>p-value</b>	<0.0001		<0.0001	
<b>HR</b>	0.45 (0.329, 0.607)		0.27 (0.171, 0.411)	

## CONCLUSIONS

The data in the PMA supplement for the BRACAnalysis CDx support the reasonable assurance of safety and effectiveness of the device when used in accordance with the indications for use. Based on the clinical efficacy report of the NOVA study, it appears that all the primary endpoints were met, and although the drug has demonstrated efficacy in both the gBRCAmut and the non-gBRCAmut cohorts, BRACAnalysis CDx™ test identifies a biomarker-defined subset of patients with a different therapeutic product effect supporting a complementary diagnostic claim of the BRACAnalysis CDx test for Zejula® (niraparib) maintenance therapy. Further, the associated clinical bridging study supports that the clinical efficacy results are maintained with the BRACAnalysis CDx test. Thus, detection of deleterious or

suspected deleterious germline BRCA variants by the BRCAAnalysis CDx test in ovarian cancer patients is associated with enhanced PFS from Zejula® (niraparib) maintenance therapy.

**RECOMMENDATION:** P140020/S009 for the BRCAAnalysis CDx test will be approved on the same day as NDA 208447 for niraparib.

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/s/  
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JEANNETTE L DININ

03/21/2017

Uploading CDRH consult memo for CDRH, Pdf is already signed by reviewers

**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: March 10, 2017

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: Morgan Walker, PharmD, MBA, CPH  
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): ZEJULA (niraparib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 208447

Applicant: TESARO, Inc.

## 1 INTRODUCTION

On October 31, 2016, TESARO, Inc. submitted for the Agency's review the final unit of a rolling submission for New Drug Application (NDA) 208447 for ZEJULA (niraparib) capsules. The proposed indication for ZEJULA (niraparib) is for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

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 November 3, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZEJULA (niraparib) capsules.

## 2 MATERIAL REVIEWED

- Draft ZEJULA (niraparib) capsules PPI received on October 31, 2016, and received by DMPP and OPDP on February 23, 2017.
- Draft ZEJULA (niraparib) capsules Prescribing Information (PI) received on October 31, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 23, 2017.

## 3 REVIEW METHODS

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

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **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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MORGAN A WALKER  
03/10/2017

NAZIA FATIMA on behalf of KEVIN WRIGHT  
03/10/2017

BARBARA A FULLER  
03/10/2017

LASHAWN M GRIFFITHS  
03/10/2017

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

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

## Memorandum

**Date:** March 9, 2017

**To:** Jeannette Dinin  
Regulatory Project Manager  
Division of Oncology Product 1  
Office of Hematology and Oncology Products

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

**Subject:** **Zejula™** (niraparib) capsules, for oral use  
NDA 208447

Office of Prescription Drug Promotion comments on proposed  
prescribing information and container label

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Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) and proposed container label for Zejula™ (niraparib) capsules, for oral use (Zejula) as requested by DOP1 in the consult dated November 3, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "NDA 208447\_substantially complete DRAFT.docx," sent by electronic mail on February 23, 2017, to OPDP (Kevin Wright) from DOP1 (Jeannette Dinin). OPDP's comments are listed in the attached PI.

OPDP also reviewed the proposed container label submitted to the electronic document room on February 8, 2017. OPDP has no comments for the proposed container label.

The combined OPDP and Division of Medical Policy Programs (DMPP) review of the patient package insert (PPI) 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](mailto:kevin.wright@fda.hhs.gov). OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/  
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KEVIN WRIGHT  
03/09/2017

## Clinical Inspection Summary

<b>Date</b>	February 28, 2017
<b>From</b>	Lauren Iacono-Connors, Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation (DCCE)
<b>To</b>	Jeannette Dinin, Regulatory Project Manager Gwynn Ison, Clinical Reviewer Division of Oncology Products 1
<b>NDA #</b>	208447
<b>Applicant</b>	Tesaro, Inc.
<b>Drug</b>	Zejula® (Niraparib)
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	Priority
<b>Proposed Indication</b>	Zejula® for the maintenance treatment of adult patients with platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are responsive to platinum-based chemotherapy.
<b>Consultation Request Date</b>	November 25, 2016
<b>Summary Goal Date</b>	February 28, 2017
<b>Action Goal Date</b>	March 31, 2017
<b>PDUFA Date</b>	June 30, 2017

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study PR-30-5011-C were submitted to the Agency in support of NDA 208447. Five clinical sites, Dr. Jonathan Berek (Site 1015), Dr. Michel Fabbro (Site 33002), Dr. Ursula Matulonis (Sites 1009 and 1009B), Dr. Mansoor Mirza (Site 45003), and the study sponsor, Tesaro, Inc., were selected for audit.

The primary efficacy endpoint, Progression Free Survival (PFS) as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Jonathan Berek, Dr. Michel Fabbro, Dr. Ursula Matulonis, Dr. Mansoor Mirza, and the study sponsor Tesaro, Inc.

### II. BACKGROUND

Tesaro, Inc. seeks approval of Niraparib for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

This clinical inspection summary request is based on the results from primarily Study PR-30-5011-C.

The following overview of the Study PR-30-5011-C is intended as background context for interpreting the inspectional findings.

Study PR-30-5011-C is a double-blind, 2:1 (niraparib:placebo) randomized, placebo-controlled evaluation of patients with platinum-sensitive, recurrent ovarian cancer who had either germline BRCA mutation or a tumor with high-grade serous or high-grade predominantly serous histology, but without such germline BRCA mutation (non-gBRCAmut) who were in response to their last platinum-based therapy. The study randomized 553 subjects at 128 clinical centers in 15 countries.

Study Period: Study initiation date (first subject enrolled): August 26, 2013  
Data cut-off date for analysis: May 30, 2016

Primary efficacy endpoint: Progression Free Survival (PFS); as determined by the clinical Investigator review of radiology data using RECIST version 1.1 criteria, defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause.

Objectives of Inspections:

- a. Verify PFS as assessed by the investigator using RECIST Version 1.1.
- b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- c. General compliance with the investigational plan.

### III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Jonathan Berek (Site 1015)</b> 300 Pasteur Drive HG-333 Stanford, CA 94305-5317	Protocol: PR-30-5011-C  Subjects: 14	February 13-17, 2017	Preliminary Classification  NAI
<b>CI#2: Ursula Matulonis (Site 1009)</b> Dana-Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215	Protocol: PR-30-5011-C  Subjects: 9	January 24-30, 2017	Preliminary Classification  NAI
<b>CI#3: Ursula Matulonis (Site 1009B)</b> Beth Israel Deaconess Medical Center 330 Brookline Avenue Boston, MA 02215	Protocol: PR-30-5011-C  Subjects: 2	February 6-7, 2017	Preliminary Classification  NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
<b>CI#4: Michel Fabbro (Site 33002)</b> 208 av. des Apothicaires Montpellier, Hérault 34298 France	Protocol: PR-30-5011-C  Subjects: 20	February 13-17, 2017	Preliminary Classification  NAI
<b>CI#5: Mansoor Mirza (Site 45003)</b> Department of Oncology 5073 Righospitalet Copenhagen Ø, Capital 2100 Denmark	Protocol: PR-30-5011-C  Subjects: 26	February 13-17, 2017	Preliminary Classification  NAI
<b>Sponsor: Tesaro, Inc.</b> 1000 Winter Street Suite 3300 Waltham, Massachusetts 02451	Protocol: PR-30-5011-C  Site Numbers: 001009, 001009B, 001015, 033002 and 045003	January 4-20, 2017	Preliminary 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.

Note: The consult request to inspect the CRO (b) (4) was cancelled by OSI/DOP 1 prior to start data.

#### **1. Dr. Jonathan Berek, M.D. (Site 1015)**

The site screened 24 subjects and enrolled 14 subjects. At the time of this inspection all 14 subjects had completed the study. A complete record review was done for all enrolled subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 208447, focusing on inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification.

Data listings were compared to and found consistent with source documents. The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. There was no evidence of under-reporting AEs. However, there were a number of minor protocol deviations, such as out-of-window follow-up visits and laboratory tests. There was one major protocol deviation. Specifically, the first dose of study drug was not administered to a subject within 72

hours of randomization. These protocol deviations were identified during the conduct of the study at this site and prior to this inspection.

The protocol deviations were appropriately addressed by the site and should not have placed subjects at undue risk or importantly impacted study outcomes.

Review of financial disclosure documentation, investigator agreements and IRB approvals found no deficiencies. Informed consent was adequately obtained for each subject.

The data from Site 1015, associated with Study PR-30-5011-C appear reliable.

## **2. Dr. Ursula Matulonis, M.D. (Site 1009)**

The site screened 17 subjects and enrolled nine subjects. At the time of this inspection one subject was still on treatment. However, this subject was enrolled at Site 1008 (Florida) and travels frequently between Florida and Massachusetts. This subject continues to receive treatment between the two sites. Regarding the nine subjects randomized at Site 1009, one subject had dropped out and eight subjects had progressed or died. A complete record review was done for all enrolled subjects and signed informed consents for all 17 screened subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 208447, focusing on inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS, was verifiable with the source records generated at the site. There was no evidence of under-reporting of AEs.

The data from Site 1009, associated with Study PR-30-5011-C, appear reliable.

## **3. Dr. Ursula Matulonis, M.D. (Site 1009B)**

The site screened and enrolled two subjects. At the time of this inspection, the two subjects were no longer on study due to disease progression. A complete record review was done for two subjects.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS, was verifiable with the source records generated at the site. There was no evidence of under-reporting of AEs.

The data from Site 1009B, associated with Study PR-30-5011-C, appear reliable.

**4. Dr. Michel Fabbro, M.D. (Site 33002)**

The site screened 29 subjects and enrolled 20 subjects. At the time of this inspection, two subjects remain on study, 16 subjects had completed the study, one subject withdrew consent and one subject was terminated early. A complete record review was done for seven subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 208447, focusing on inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. There was no evidence of under-reporting AEs.

The data from Site 33002, associated with Study PR-30-5011-C appear reliable.

**5. Dr. Mansoor Mirza, M.D. (Site 45003)**

The site screened 30 subjects and enrolled 26 subjects. At the time of this inspection, 23 subjects had completed the study. A complete record review was done for nine subjects. The inspection included assessments of primary efficacy data, adverse events, serious adverse events, laboratory results (CA125, AST, ALT, GGT, hemoglobin, creatinine and bilirubin), randomization, Informed Consent Forms, entry criteria compliance, Form FDA 1572 history, and financial disclosure compliance.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. With two minor exceptions, there was no evidence of under-reporting AEs. Subject 045003-00001 had an upper respiratory infection and Subject 045003-00008 reported diarrhea. The clinical investigator indicated corrective actions would be taken following the close out of the inspection.

The data from Site 45003, associated with Study PR-30-5011-C appear reliable.

**6. Sponsor: Tesaro, Inc.**

The inspection focused on the sponsor's control, oversight, and management of Study PR-30-5011-C. Records reviewed included but were not limited to organizational charts, vendor list, vendor oversight plans, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, safety reports, AE's/SAE's, protocol deviations, standard operating procedures (SOP's), electronic Case Report Forms (e-CRF's), and test article documentation. Obligations of responsibilities were shared and/or transferred to the Contract Research Organization (CRO) [REDACTED] (b)(4). There was evidence of sponsor oversight of all obligations. Monitoring records were reviewed from five clinical sites (001009, 001009B, 001015, 033002 and 045003).

Tesaro maintained adequate oversight over the study. The inspection revealed no significant deficiencies. There was no evidence of under-reporting AEs.

Tesaro contracted with (b) (4) to conduct monitoring. Monitoring reports that showed issues at study sites were immediately followed by oversight procedures that brought sites back into compliance. All aspects of this study had Tesaro personnel in an oversight position.

Reporting practices for AEs and SAEs were also reviewed. The primary efficacy endpoint, PFS, per RECIST1.1, as determined by the Blinded Independent Radiology Center (BIRC) was not verified during this inspection. All efficacy source records generated by the BIRC remain with the vendor, (b) (4). However, all other sponsor-related responsibilities that were carried out by (b) (4) were reviewed during the sponsor inspection. No deficiencies were noted.

The data from this sponsor submitted to the Agency associated with Study PR-30-5011-C appear reliable.

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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}

Susan Thompson, M.D.  
Team Leader  
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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA #208447  
DOP1/Division Director/Geoffrey Kim  
DOP1/Clinical Team Leader/Laleh Amiri  
DOP1/Project Manager/Jeanette Dinin  
DOP1/Medical Officer/Gwynn Ison  
OSI/Office Director (Acting)/David Burrow  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/Branch Chief/Kassa Ayalew  
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

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LAUREN C IACONO-CONNORS  
02/28/2017

SUSAN D THOMPSON  
02/28/2017

KASSA AYALEW  
02/28/2017

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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)

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**Date of This Memorandum:** February 15, 2017  
**Requesting Office or Division:** Division of Oncology Products 1 (DOP1)  
**Application Type and Number:** NDA 208447  
**Product Name and Strength:** Zejula (niraparib) capsules, 100 mg  
**Submission Date:** February 8, 2017  
**Applicant/Sponsor Name:** Tesaro, Inc.  
**OSE RCM #:** 2016-2454-1  
**DMEPA Primary Reviewer:** Tingting Gao, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

#### 1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised Zejula container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

Additionally, Tesaro clarified that the two data matrix (2-D barcode) codes contain the following information:<sup>b</sup>

1. The data matrix code on the left is the serialized code that holds the GTIN, lot, exp, and serial number specific to the product.
2. The smaller data matrix code on the right is needed by our packager ( (b) (4) ) for the vision system on their packaging line and will encode their item/part number. Tesaro has moved the entire "FPO" area down for increased barcode scanability on the line.

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<sup>a</sup> Gao T. Label and Labeling Review for Zejula (NDA 208447). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 12. 6 p. OSE RCM No.: 2016-2454.

<sup>b</sup> Tesaro. NDA 208447 Zejula (niraparib): Response to Information Request (Bottle Label). Waltham (MA): Tesaro, Inc. 2017 FEB 8.

## **2 CONCLUSION**

The revised Zejula container label is acceptable from a medication error perspective. We have no further recommendations at this time.

### **APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBURARY 8, 2017**

#### **Container label**

(b) (4)



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02/15/2017

CHI-MING TU  
02/15/2017

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

<b>IND or NDA</b>	NDA 208447
<b>Brand Name</b>	Zejula
<b>Generic Name</b>	Niraparib
<b>Sponsor</b>	TESARO, Inc.
<b>Indication</b>	Treatment of adult patients with platinum sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.
<b>Dosage Form</b>	Capsule
<b>Drug Class</b>	PARP 1 and 2 inhibitor
<b>Therapeutic Dosing Regimen</b>	300 mg QD
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	300 mg QD
<b>Submission Number and Date</b>	SDN003; Nov 3 2016
<b>Review Division</b>	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**

The data from Study PR-30-5015-C (NOVA) excluded a large mean QTc prolongation effect (20 ms) at the therapeutic exposures with 300 mg QD dosing of niraparib. The concentration-QTc analysis showed that the largest upper bound of the 2-sided 90% CI for  $\Delta\Delta\text{QTcF}$  at the steady state mean  $C_{\text{max}}$  corresponding to the therapeutic dose (300 mg QD) of niraparib was 10 ms (Table 1). This result is supported by the by-time central tendency analysis (Table 2). The study did not include a positive control (moxifloxacin) and assay sensitivity could not be established. As per the ICH E14 Q&A (R3), 6.1, “In the absence of a positive control, there is reluctance to draw conclusions of lack of an effect; however, if the upper bound of the two-sided 90% confidence interval around the estimated maximal effect on QTc is less than 10 ms, it is unlikely to have an actual mean effect as large as 20 ms”.

The Study PR-30-5015-C (NOVA) was a randomized, double-blind, placebo-controlled study with 367 patients on 300 mg QD dosing of niraparib and 179 patients on placebo. The effect of niraparib on QT prolongation was evaluated with only the therapeutic dose (300 mg QD), which was deemed the maximum tolerated dose. The central tendency analysis and concentration-QTc analysis quoted above is based on the data from this

NOVA Main Study where ECG/PK assessments were done in all patients at baseline, 2 h post dose on Cycle 1 Day 1 and pre-dose and at 2 h post-dose on Cycle 2 Day 1.

There was a QTc substudy with intensive PK/ECG assessment in 26 subjects (and additional similar assessment in 15 subjects in NOVA Main Study) that was submitted as a part of QTc evaluation. However, the data from the substudy was limited by inadequate ECG sampling on Cycle 1 Day 1 (collected over 8 h after single dose which is unable to detect delayed effects) and inadequate drug exposure (at steady state niraparib  $C_{max}$  accumulates by 1.8-fold).

**Table 1: Niraparib  $\Delta$ QTcF and  $\Delta\Delta$ QTcF estimates at the steady state mean  $C_{max}$  for the therapeutic dosing of 300 mg QD**

Exposure	Parameter	Concentration ( $\mu$ g/ml)	Estimate	Lower 90% CI	Upper 90% CI
Steady State $C_{max}$	$\Delta$ QTcF	1.2	5.8	1.6	10.0
	$\Delta\Delta$ QTcF	1.2	3.8	-1.0	8.7

**Table 2: Niraparib  $\Delta$ QTcF and  $\Delta\Delta$ QTcF estimates using the by-time central tendency analysis (FDA Analysis)**

	Placebo			300 mg Niraparib				
	$\Delta$ QTcF			$\Delta$ QTcF			$\Delta\Delta$ QTcF	
Visit	N	Mean (ms)	90% CI (ms)	N	Mean (ms)	90% CI (ms)	Mean Diff. (ms)	90% CI (ms)
CYCLE 1 DAY 1	167	-1.8	(-6.9, 3.2)	348	3.6	(1.2, 5.9)	5.4	(-0.2, 11.0)
CYCLE 2 DAY 1	162	4.7	(1.8, 7.6)	275	3.5	(0.3, 6.7)	-1.2	(-5.4, 3.1)

The dose of 300 mg evaluated in this QT study is the therapeutic dose and the maximum tolerated dose. Thus studying higher doses is not feasible. The timing of the ECGs on day 1 after a single dose is not acceptable because the exposure of niraparib is not at steady-state. Niraparib has ~1.8-fold higher  $C_{max}$  at steady state with multiple dosing compared to a single dose. Mild and moderate renal and hepatic impairment does not have clinically important effects on niraparib pharmacokinetics based on a population PK analysis. The effect of severe hepatic and renal impairment on niraparib pharmacokinetics has not been studied. Clinical drug-drug interaction (DDI) studies for niraparib have not been conducted. Concomitant administration of a high fat meal results in ~21% decrease in  $C_{max}$  compared to fasted state, but no significant change in AUC after administration of 300 mg of niraparib.

## 2 PROPOSED LABEL

The sponsor did not include any QT-related language in their current proposed label. The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

The potential for QTc prolongation with niraparib was evaluated in a randomized, placebo-controlled trial in cancer patients (367 patients on niraparib and 167 patients on placebo). No large changes in the mean QTc interval (>20 ms) were detected in the trial following the treatment of niraparib 300 mg once daily.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Niraparib is an orally available, potent, highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway and as a sensitizing agent in combination with cytotoxic agents and radiotherapy.

### 3.2 MARKET APPROVAL STATUS

Niraparib is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

In a non-GLP in-vivo safety pharmacology study (TT#07-5300), niraparib was administered intravenously (IV) during 3 sequential 30-minute periods at 1, 3, and 10 mg/kg to determine its effect on cardiovascular function in 3 anesthetized, vagotomized dogs. Heart rate, mean arterial pressure, and electrocardiographic parameters (PR, QRS, and QT/QTc intervals) were monitored predose and during each 30-minute infusion period. There was no effect on QT/QTc, blood flow or PR up to and including the highest dose of 10 mg/kg. At that dose, the peak average plasma concentration measured during infusion in dogs was  $15.3 \pm 1.1 \mu\text{M}$  (4896 ng/mL total bound and unbound). Niraparib increased the heart rate in a dose-dependent fashion (+5%, +9%, and +17%). A dose-independent increase (+16% to +21%) in mean arterial pressure was observed from 1 mg/kg. A small increase in the QRS interval (+6%) was observed at 10 mg/kg only. Peak average plasma concentrations (total bound and unbound) measured during infusion of the 1, and 3 mg/kg doses were  $1.2 \mu\text{M}$  (384 ng/mL) and  $3.9 \mu\text{M}$  (1248 ng/mL) at the 1 and 3 mg/kg dose levels, respectively.

In the 1-month and 3-month GLP toxicity studies in dogs, niraparib was administered at the highest doses of 15 and 12 mg/kg/day, respectively. ECGs were monitored in these conscious dogs. No treatment related ECG abnormalities were observed.

Safety pharmacology studies have shown that niraparib inhibited the rapid component of the delayed rectifier potassium current (IKr) ion channel in vitro (hERG [human-ether-a-go-go] assay) with an IC50 value of 10  $\mu\text{M}$ .

### 3.4 PREVIOUS CLINICAL EXPERIENCE

The safety, tolerability, and PK of niraparib has been evaluated in a series of clinical studies including single- and multiple-dose PK (PN001), AME (PR-30-5015-C), and the pivotal Phase 3 NOVA study, with the addition of 2 substudies, the QTc (PR-30-5011-C1-QTC) and food effect (PR-30-5011-C2-FE), for an overall niraparib-dosed population of 526 patients.

In the Phase 1 dose escalating study (PN001), 12 of the 104 (11.5%) patients were reported to experience QT prolongation; 7 of those 12 (58.3%) patients were receiving niraparib 300 mg QD (the recommended Phase 2 dose). No events of Torsades de Pointes (TdP), sudden death, or other significant cardiac sequelae reported in the patients with prolonged QT.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of niraparib’s clinical pharmacology.

## 4 SPONSOR’S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 100996. The reviewers noted the inadequacy of timing of ECG collection as follows: “We do not agree with the timing of the ECGs on Day 1 because niraparib is not at steady-state. Niraparib has shown 2- to 3-fold accumulation. Triplicate ECGs should be obtained over a 24-hour period on a study day in which steady state has been reached.”<sup>1</sup>

The sponsor submitted concentration and QTc data from three studies to evaluate the effects of niraparib on cardiac repolarization following a single dose and to correlate changes from baseline in QTc with niraparib concentrations in patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. A summary of the three studies is provided in Table 3.

The sponsor has also collected limited data on Day 1 of Cycle 1 (baseline and 2 h post-dose) and Day 1 of Cycle 2 (predose and 2 h post-dose) in all the subjects in the NOVA Main Study (Table 3; shaded in grey color). Since there was inadequate exposure margin with ECG assessment on Day 1 in the QTc substudy and food effect study, the reviewers also evaluated this data from entire NOVA Main Study to evaluate possible exclusion of large QTc prolongation signal (20 ms).

**Table 3: Summary of studies that are included in this QT-IRT review**

	Study Design	Dose: # Subjects	PK/ECG Sampling Schedule
PR-30-5011-C1, QTc substudy	Open-label	300 mg QD: 26	Time-matched triplicate ECG/PK:
PR-30-5015-C, NOVA sub study (patients in main study with similar ECG/PK assessments as QTc substudy)	Double-blind, randomized, placebo controlled	300 mg QD: 10 Placebo: 5	Cycle 1/Day 1 pre-dose and 1, 1.5, 2, 3, 4, 6 and 8 hours post-dose.  Additional single 12-lead ECG and PK: Cycle 2/Day 1

			predose and 2 hours postdose
PR-30-5011-C2, FE substudy	Open-label, 2-treatment, 2-sequence crossover, single dose	300 mg: 17	Time-matched triplicate ECG/PK: Days 1 and 8 at baseline and at 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose
PR-30-5015-C, NOVA main study (All patients)	Double-blind, randomized, placebo controlled	300 mg QD: 367 Placebo: 179	Time-matched single 12-lead ECG and PK: Baseline, Cycle 1/Day 1 two hours postdose and Cycle 2/Day 1 predose and two hours postdose

## 4.2 QT STUDY

### 4.2.1 Title

Evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

### 4.2.2 Protocol Number

PR-30-5011-C (NOVA Main Study);

PR-30-5011-C1 (QTc substudy);

PR-30-5011-C2 (NOVA Food Effect substudy)

### 4.2.3 Study Dates

First patient enrolled (signed informed consent): 26 August 2013 (NOVA Main Study), 1 April 2015 (QTc substudy), 5 August 2013 (NOVA food effect substudy)

Last patient completed: 20 October 2015 for NOVA food effect study and study is ongoing for the other.

Release date of report: 24 September 2016 (NOVA Main Study), 23 September 2016 (QTc substudy) and 27 September 2016 (food effect substudy)

### 4.2.4 Objectives

One of the objectives is to evaluate effect on QTc in niraparib-treated ovarian cancer patients.

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<sup>1</sup> DARRTS: IND 100996: CONSULT REV-QTIRT-01 (QT-IRT Review), 07/09/2013, by Kevin Krudys

## 4.2.5 Study Description

### 4.2.5.1 Design

Study PR-30-5011-C, also known as NOVA, is a double-blind, 2:1 (niraparib:placebo) randomized, placebo-controlled evaluation of patients with platinum-sensitive, recurrent ovarian cancer who had either germline BRCA mutation or a tumor with high-grade serous or high-grade predominantly serous histology, but without such germline BRCA mutation (non-gBRCAmut) who were in response to their last platinum-based therapy. Enrollment into the cohorts was determined by the results of Myriad's Integrated BRCAAnalysis® testing. Randomization was stratified by time to progression after the penultimate platinum therapy before study enrollment (6 to <12 months or ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no); and best response during the last platinum regimen (complete response [CR] or partial response [PR]).

Study PR-30-5011-C1, also known as NOVA QTc substudy, is an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. This substudy was initiated at US Amendment 1 (03 March 2015).

In both the above protocols, enrolled patients were treated with niraparib 300 mg as QD dosing on Cycle 1/Day 1 and beyond.

Study PR-30-5011-C2, was Food Effect Substudy, in which patients at 6 sites in the US were enrolled into a 14-day, open-label, 2-treatment, 2-sequence crossover substudy to evaluate the effect of a high-fat meal on niraparib (single-dose) exposure. Eligibility criteria from the NOVA main study were broadened for the FE substudy to include patients with ovarian cancer, regardless of platinum sensitivity and burden of disease, as long as no standard therapy existed or the patient refused standard therapy. Patients were randomized to either Sequence AB or Sequence BA. In Sequence AB, patients fasted (nothing to eat or drink, except water) for at least 10 hours before receiving a single dose of 300 mg niraparib, and continued to fast for at least 2 hours following the dose. In Sequence BA, patients fasted for at least 10 hours before consuming a high-fat meal; within 5 minutes of finishing the meal, a single dose of 300 mg niraparib was administered orally and patients resumed fasting for at least 4 hours. After a 7-day PK assessment and wash-out period, all patients received their second single dose of niraparib on Day 8 under the opposite conditions: Sequence AB patients received niraparib after a high-fat meal and Sequence BA patients received niraparib under fasting conditions.

### 4.2.5.2 Controls

Placebo and positive controls were not used in the NOVA QTc substudy and food effect study.

There was placebo control, but no positive control in NOVA Main Study.

### 4.2.5.3 Blinding

NOVA QTc substudy and food effect study were open-label studies while NOVA Main Study was a double-blind study.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

In drug treatment arm of NOVA Main Study and QTc substudy, niraparib 300 mg (3 x 100 mg niraparib capsules) was administered orally QD continuously until cancer progression, intolerable toxicity, or patient or investigator determination. Patients randomized to placebo received 3 appearance-matched placebo capsules QD orally.

In food effect study, patients received a single dose of 300 mg niraparib on Day 1 and Day 8 (with high-fat meal on one of these two days and in fasting state on the other day).

### 4.2.6.2 Sponsor's Justification for Doses

Niraparib 300 mg (3 x 100 mg niraparib capsules) was administered orally QD continuously until cancer progression, intolerable toxicity, or patient or Investigator determination. The dose is based upon the dose-escalating Phase 1 study (PN001) in patients with advanced cancer; the study established 300 mg once daily to be the maximal tolerated dose in patients with advanced cancer. Patients were instructed to take their dose at the same time of the day, preferably in the morning, and to swallow all capsules whole without chewing. Water consumption with dose administration was permissible. Each patient's first dose was administered at the study site.

*Reviewer's Comment: Acceptable. The 300 mg QD is the therapeutic dose and the maximum tolerated dose; therefore, higher doses cannot be studied.*

### 4.2.6.3 Instructions with Regard to Meals

Patients enrolled in NOVA Main Study or the QTc substudy were not required to fast prior to dosing.

The food-effects (FE) substudy was a cross-over study design; patients either fasted or ate a high fat meal prior to dosing, then after a 7 day washout period were dosed under the opposite state.

*Reviewer's Comment: The impact of fed state on PK is limited with  $C_{max}$  in fed state lower than that in fasted state by 21.5%.*

### 4.2.6.4 ECG and PK Assessments

Refer to Table 3 above.

*Reviewer's Comment: Although the ECG/PK sampling in QT substudy and food effect study covers the  $T_{max}$  (2-4 h), the overall ECG assessment just on Cycle 1 Day 1 after the single dose in these studies is not adequate because niraparib is not at steady-state. The  $C_{max}$  at steady state after multiple dosing of 300 mg QD is expected to be 1.8-fold of the  $C_{max}$  after the single dose. Furthermore, the sampling is limited to 8 h post-dose and does not cover any potential delayed effects. Because there was inadequate exposure margin with ECG assessment on Day 1 in the QTc substudy and food effect study, the reviewers*

also evaluated the ECG/PK data collected from Cycle 1 Day 1 and Cycle 2 Day 1 (which represents steady state) in all patients in NOVA Main Study to evaluate possible exclusion of large QTc prolongation signal (20 ms).

#### **4.2.6.5 Baseline**

Pre-dose baseline was used.

#### **4.2.7 ECG Collection**

In addition to the standard 12-lead ECG conducted at screening, Cycle 1/Day 1 and Cycle 2/Day 1 (predose and 2 hours postdose) and at the study treatment discontinuation visit, patients selected for intensive ECG monitoring underwent ECG monitoring to coincide with PK sampling on Day 1 at predose and at 1, 1.5, 2, 3, 4, 6 and 8 hours postdose. For this intensive ECG monitoring subset, triplicate ECGs were performed between 2 and 5 minutes apart and prior to PK blood draws. Patients were to be supine and rested for approximately 2 minutes before ECGs were recorded.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A subset of patients from the NOVA main study, patients from the FE substudy, and a separate set of patients enrolled specifically in the QTc substudy were included in the QTc population (total N=58 patients). These patients underwent intensive ECG monitoring concurrent with blood sampling for determination of niraparib plasma concentrations.

NOVA Main Study:

At the time of the data cutoff of 30 May 2016, 274 (74%) of all 372 patients who were randomized to niraparib had discontinued from treatment as had 163 (90%) of the 181 patients randomized to placebo.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

Primary analysis is exposure response. Please refer to section 4.2.8.4.

###### **4.2.8.2.2 Assay Sensitivity**

There is no assay sensitivity analysis performed. This study was open-label, and no control group was used.

###### **4.2.8.2.3 Categorical Analysis**

**Table 4: Categorical Analysis of QTcF**

Parameter Category of Change	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
<b>Maximum post-baseline QTcF Interval</b>		
>450 ms	42 (11.4)	29 (16.2)
>480 ms	7 (1.9)	1 (0.6)
>500 ms	5 (1.4)	0
<b>Change from baseline to maximum post-baseline QTcF Interval</b>		
>30 ms	50 (13.6)	22 (12.3)
>60 ms	10 (2.7)	5 (2.8)

Source: Sponsor's Niraparib TESARO PR-30-5011-C (NOVA) Main Clinical Study Report page 256

#### 4.2.8.3 Safety Analysis

NOVA Main Study:

There were no on-treatment deaths reported during the study. Two deaths related to MDS that occurred in the post-treatment period, 1 each in the niraparib and placebo arms, were assessed as treatment-related by the Investigators.

Overall 110 (30%) of 367 patients treated with niraparib and 27 (15%) of 179 patients who received placebo reported an SAE.

The most common SAEs were thrombocytopenia and anemia. Thrombocytopenia was reported as an SAE in 40 patients (11%) who received niraparib and anemia was reported in 14 (4%); none of the patients who received placebo reported serious events of thrombocytopenia or anemia. All other SAEs were reported in <2% of niraparib-treated patients.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results from the food effect substudy are presented in Table 5.  $AUC_{0-last}$  and  $AUC_{0-\infty}$  were demonstrated to be bioequivalent under fast and fed conditions. The fed to fasted ratio for  $C_{max}$  was determined to be 78.5% and the 90% confidence interval was 69.5% to 88.6%.

**Table 5: Summary of Niraparib Plasma PK Parameters by Treatment**

Treatment		t <sub>1/2</sub> (hr)	t <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>0-last</sub> (ng*hr/mL)	AUC <sub>0-∞</sub> (ng*hr/mL)
Fasting	N <sup>1</sup>	16	16	16	16	15
	Mean	50.5	3.5	803.7	28638.1	29016.1
	SD	17.87	1.19	403.35	17911.86	18405.23
	Min	30.2	1.7	177	7128.5	7695.3
	Median	46.4	3.1	766.5	24570.9	26862.9
	Max	99.4	6.1	1440	68851	71416.2
	CV%	35.4	33.6	50.2	62.5	63.4
Fed	N <sup>1</sup>	14	15	15	15	14
	Mean	47.9	8	582.1	27186.4	31194
	SD	17.54	4.91	228.57	14111.37	16894.88
	Min	34.9	1.2	222	11761	12665.2
	Median	42.5	6.1	585	20765	25267.8
	Max	105.5	23	1080	52659.3	60444.1
	CV%	36.7	61.1	39.3	51.9	54.2

Source: Applicant's study report PR-30-5011-C2 page 67, Table 8

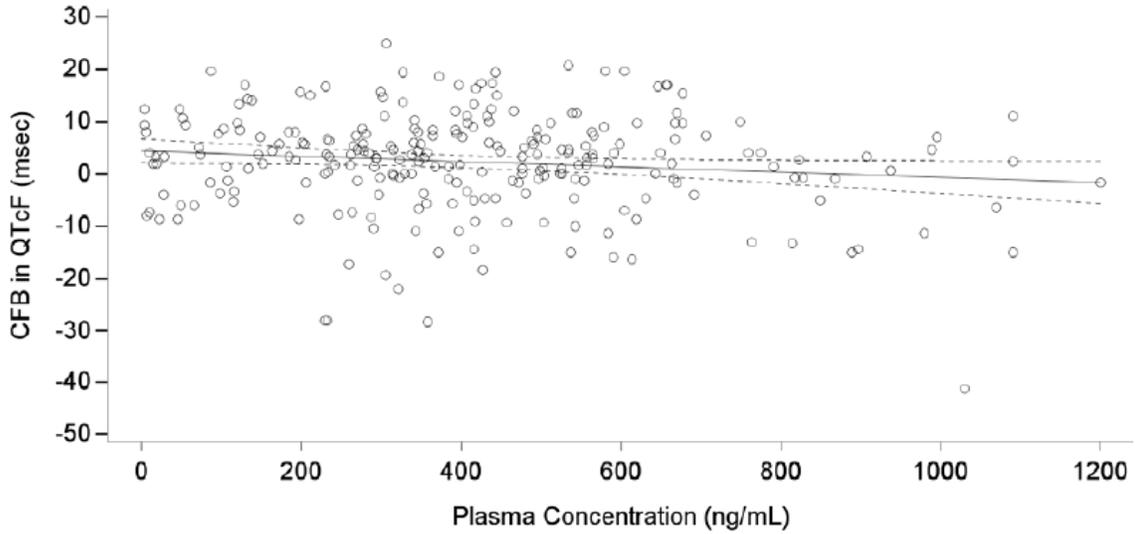
Reviewer's Comment: The PK results for the NOVA main study and the QTc substudy cannot be located in the applicant's study reports. Reviewer's analysis presenting the relevant PK information is included in Section 5.3.

#### 4.2.8.4.2 Exposure-Response Analysis

The PK-ΔQTcF analyses were conducted using the dataset including (1) subjects from the NOVA main study who participated in intensive ECG monitoring and subjects from the QTc substudy, (2) a dataset with subjects from the food effect (FE) substudy, and (3) the combined dataset from the NOVA main, QTc and FE substudies. A linear mixed model with an intercept was considered as the primary analysis and the results are presented in Figure 1, Figure 2, and Figure 3. The estimated slope was 0.0014 with a 95% CI of -0.0055 to 0.0092 and a p-value of 0.544 for the analysis with NOVA main study and QTc substudy data. The estimated slope was -0.0002 with a 95% CI of -0.006 to 0.0055 and a p-value of 0.936 for the analysis with food effect substudy data. The estimated slope was 0.0049 with a 95% CI of -0.002 to 0.0117 and a p-value of 0.164 for the analysis with combined ECG data.

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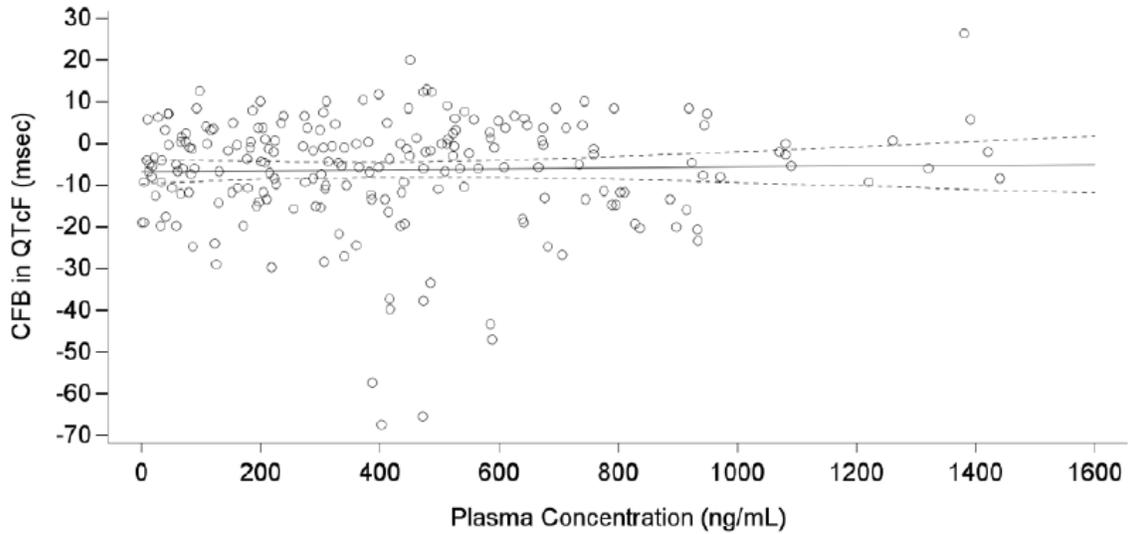
**Figure 1: Change from Baseline in QTcF Regressed against Plasma Concentration - NOVA Main and QTc Substudy**



Regression line (95% CI): Intercept = 1.7, Slope = 0.0014(-0.0031, 0.0060),  $p=0.544$  for the slope of CFB in QTc against plasma concentration, which are calculated from a mixed effects model with a fixed effect for plasma concentration and random effect for subject.

Source: Applicant's study report PR-30-5011-C1-CS page 42, Figure 4

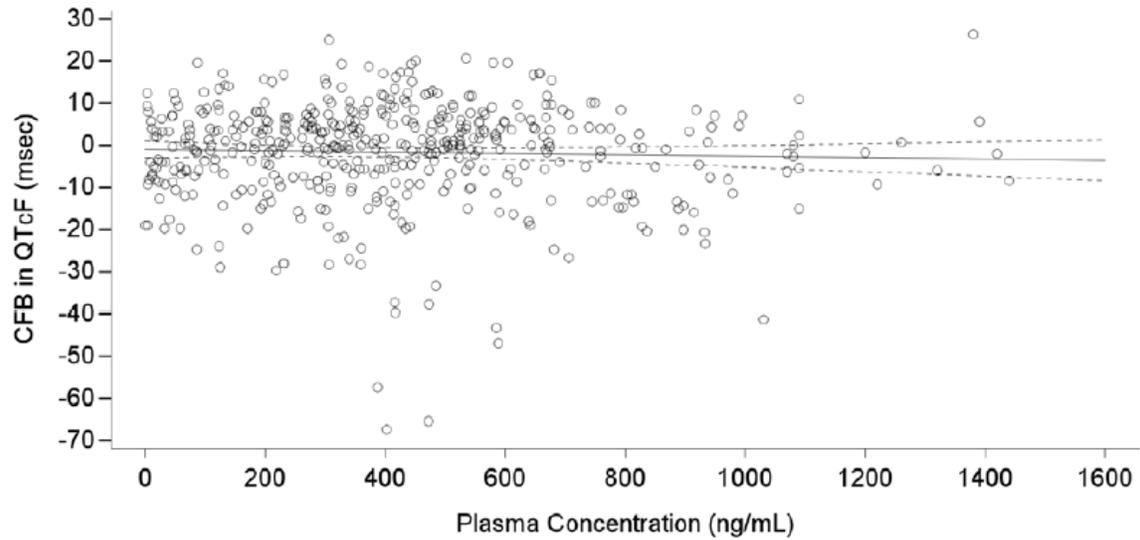
**Figure 2: Change from Baseline in QTcF Regressed against Plasma Concentration - Food Effect Substudy**



Regression line (95% CI): Intercept = -5.8, Slope = -0.0002(-0.0060, 0.0055),  $p=0.936$  for the slope of CFB in QTc against plasma concentration, which are calculated from a mixed effects model with a fixed effect for plasma concentration and random effect for subject.

Source: Applicant's study report PR-30-5011-C1-CS page 51, Figure 6

**Figure 3: Change from Baseline in QTcF Regressed against Plasma Concentration- Combined ECG Data**



Regression line (95% CI): Intercept = -2.2, Slope = 0.0049(-0.0020, 0.0117),  $p=0.164$  for the slope of CFB in QTc against plasma concentration, which are calculated from a mixed effects model with a fixed effect for plasma concentration and random effect for subject.

Source: Applicant's study report PR-30-5011-C1-CS page 21, Figure 7

Reviewer's Analysis: Reviewer's independent analysis plot of  $\Delta QTcF$  vs. drug concentrations is presented in Section 5.3.

## 5 REVIEWERS' ASSESSMENT

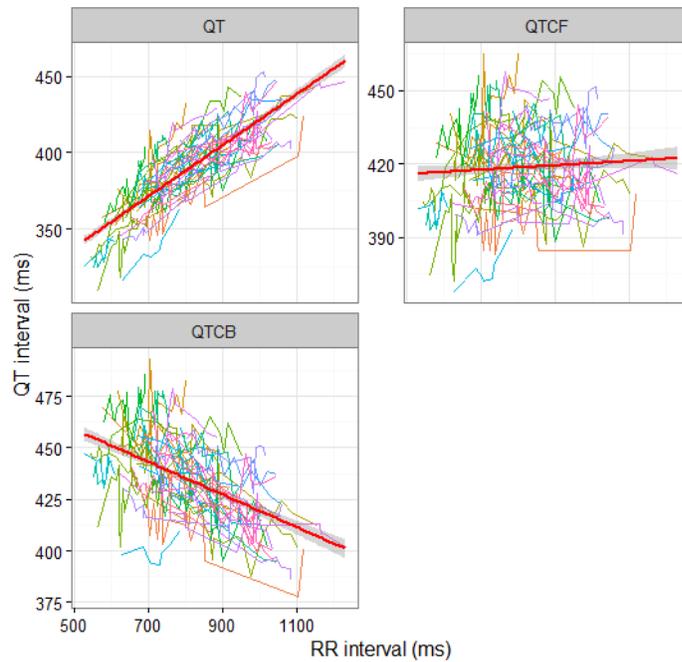
### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

QTcF is used in central tendency analysis and categorical analysis.

The relationship between different correction methods and RR is presented in Figure 4.

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**Figure 4: 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 Central Tendency Analysis

**Combined substudy dataset:** The descriptive summary of  $\Delta$ QTcF at Day 1 is listed in the following table.

**Table 6: Descriptive Summary of  $\Delta$ QTcF at Day 1**

Treatment	TIME	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
300 mg Niraparib	1	52	-0.8	10.98	-3.3	1.8
	1.5	49	0.7	10.74	-1.9	3.3
	2	52	0.6	10.17	-1.7	3.0
	3	52	1.4	11.41	-1.2	4.1
	4	52	0.1	12.72	-2.9	3.0
	6	52	-2.3	13.96	-5.6	0.9
	8	52	-1.6	14.07	-4.8	1.7
Placebo	1	4	3.0	9.36	-8.0	14.0
	1.5	4	3.4	6.62	-4.4	11.2

	2	4	0.3	5.70	-6.5	7.0
	3	4	3.4	4.03	-1.3	8.2
	4	4	0.2	6.87	-7.9	8.2
	6	4	-1.3	5.08	-7.2	4.7
	8	4	-0.7	6.63	-8.5	7.1

**NOVA Main Study:** The descriptive summary of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF at 2 hour postdose by visit (Cycle 1 Day 1 and Cycle 2 Day 1) is listed in the following table.

**Table 7: Descriptive Summary of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF**

	Placebo			300 mg Niraparib				
	$\Delta$ QTcF			$\Delta$ QTcF			$\Delta\Delta$ QTcF	
Visit	N	Mean (ms)	90% CI (ms)	N	Mean (ms)	90% CI (ms)	Mean Diff. (ms)	90% CI (ms)
CYCLE 1 DAY 1	167	-1.8	(-6.9, 3.2)	348	3.6	(1.2, 5.9)	5.4	(-0.2, 11.0)
CYCLE 2 DAY 1	162	4.7	(1.8, 7.6)	275	3.5	(0.3, 6.7)	-1.2	(-5.4, 3.1)

### 5.2.1.2 Categorical Analysis

**Combined substudy dataset:** The table below lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 8: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	52	466	46 (88.5%)	453 (97.2%)	6 (11.5%)	13 (2.8%)
Placebo	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)

**NOVA Main Study:** Table 9 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. There are 6 subjects with QTcF was above 480 ms in 300 mg Niraparib group.

**Table 9: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms		480 ms<Value $\leq$ 500 ms		Value>500	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	362	627	323 (89.2%)	580 (92.5%)	33 (9.1%)	39 (6.2%)	2 (0.6%)	3 (0.5%)	4 (1.1%)	5 (0.8%)
Placebo	171	329	149 (87.1%)	302 (91.8%)	22 (12.9%)	27 (8.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

**Combined substudy dataset:** The table below lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms	
	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	52	466	52 (100%)	466 (100%)
Placebo	4	28	4 (100%)	28 (100%)

**NOVA Main Study:** Table 11 lists the categorical analysis results for  $\Delta$ QTcF. There are 6 subjects with change from baseline values above 60 ms in 300 mg Niraparib group.

**Table 11: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	359	623	318 (88.6%)	576 (92.5%)	35 (9.7%)	40 (6.4%)	6 (1.7%)	7 (1.1%)
Placebo	170	327	155 (91.2%)	309 (94.5%)	12 (7.1%)	15 (4.6%)	3 (1.8%)	3 (0.9%)

### 5.2.2 HR Analysis

**Combined substudy dataset:** The outlier analysis results for HR are presented in table below. There are 7 subjects who experienced HR interval greater than 100 bpm in 300 mg Niraparib group.

**Table 12: Categorical Analysis for HR**

Treatment Group	Total N		Value<=100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	52	466	45 (86.5%)	438 (94.0%)	7 (13.5%)	28 (6.0%)
Placebo	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)

**NOVA Main Study:** The outlier analysis results for HR are presented in Table 13. There are 31 subjects who experienced HR interval greater than 100 bpm in 300 mg Niraparib group.

**Table 13: Categorical Analysis for HR**

Treatment Group	Total N		Value<=100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	373	650	342 (91.7%)	617 (94.9%)	31 (8.3%)	33 (5.1%)
Placebo	175	340	170 (97.1%)	335 (98.5%)	5 (2.9%)	5 (1.5%)

### 5.2.3 PR Analysis

**Combined substudy dataset:** The outlier analysis results for PR are presented in table below. There are 2 subjects who experienced PR interval greater than 200 ms in 300 mg Niraparib group.

**Table 14: Categorical Analysis for PR**

Treatment Group	T		Value<=200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	52	466	50 (96.2%)	458 (98.3%)	2 (3.8%)	8 (1.7%)
Placebo	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)

**NOVA Main Study:** The outlier analysis results for PR are presented in Table 15. There are 18 subjects who experienced PR interval greater than 200 ms in 300 mg Niraparib group.

**Table 15: Categorical Analysis for PR**

Treatment Group	Total N		Value<=200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	372	650	354 (95.2%)	627 (96.5%)	18 (4.8%)	23 (3.5%)
Placebo	173	332	161 (93.1%)	315 (94.9%)	12 (6.9%)	17 (5.1%)

#### 5.2.4 QRS Analysis

**Combined substudy dataset:** The outlier analysis results for QRS are presented in table below. There is 1 subject who experienced QRS interval greater than 110 ms in 300 mg Niraparib group.

**Table 16: Categorical Analysis for QRS**

Treatment Group	T		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	52	466	49 (94.2%)	448 (96.1%)	2 (3.8%)	17 (3.6%)	1 (1.9%)	1 (0.2%)
Placebo	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

**NOVA Main Study:** The outlier analysis results for QRS are presented in Table 17. There are 13 subjects who experienced QRS interval greater than 110 ms in 300 mg Niraparib group.

**Table 17: Categorical Analysis for QRS**

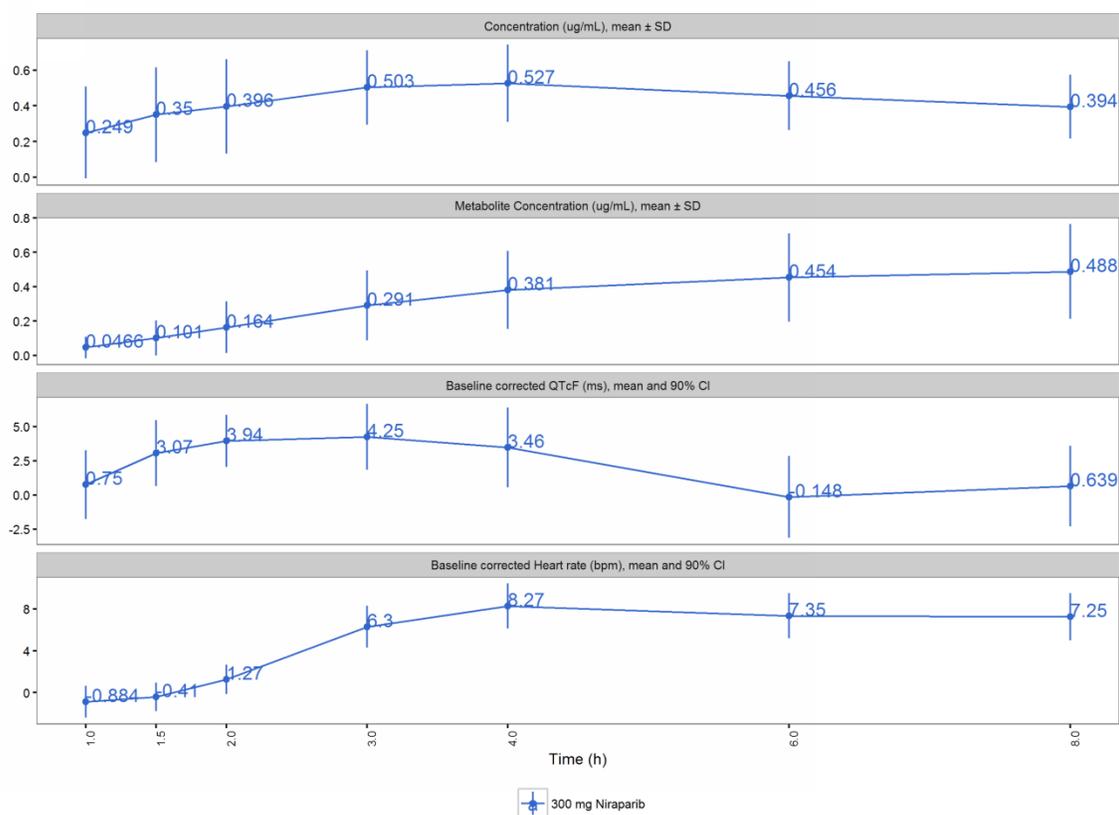
Treatment Group	T		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
300 mg Niraparib	374	653	336 (89.8%)	608 (93.1%)	25 (6.7%)	30 (4.6%)	13 (3.5%)	15 (2.3%)
Placebo	176	341	150 (85.2%)	302 (88.6%)	16 (9.1%)	24 (7.0%)	10 (5.7%)	15 (4.4%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

#### Assessment with data from QTc substudy (and some subjects in NOVA main study with similar assessments as QTc substudy)

For the reviewer's assessment, only data with intensive sampling from NOVA main study and QTc substudy was analyzed (food effect study was excluded due to study design differences) to evaluate heart rate/QTcF effects after first dose of niraparib on Cycle 1 Day 1. Placebo data was also excluded because there were only 4 subjects, which is inadequate to characterize and account for the placebo effect. Figure 5 shows the comparison of time profiles for drug concentration, metabolite concentration,  $\Delta$ QTcF and  $\Delta$ HR on Cycle 1 Day 1 to evaluate presence of any time delay between concentration and QTc interval and to evaluate any heart rate effects. There does not seem to be any significant delayed effect on QTcF changes.

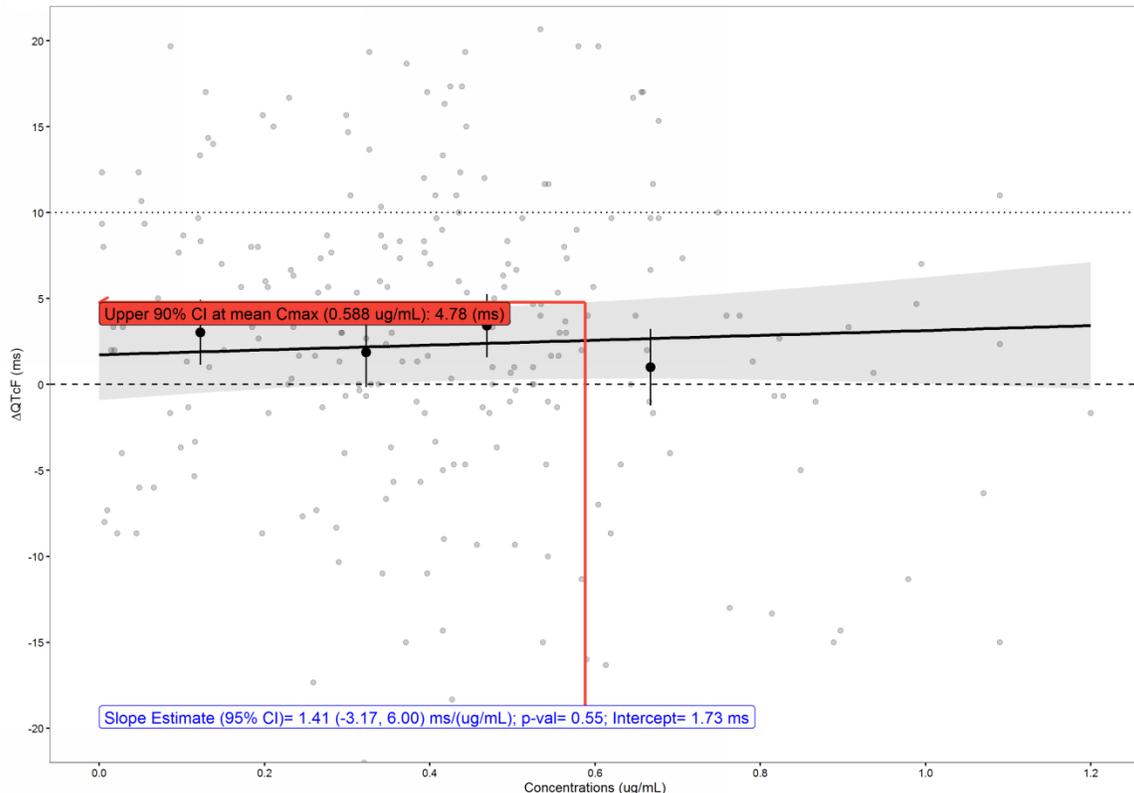
**Figure 5: Drug concentration, metabolite concentration,  $\Delta$ QTcF, and  $\Delta$ HR plotted on the same time axis (on Cycle 1 Day 1). Error bars illustrate mean  $\pm$  SD for concentration and 90% CI for  $\Delta$ HR and  $\Delta$ QTcF**



Also the relationship between  $\Delta$ QTcF and niraparib plasma concentration was evaluated using a liner mixed effects model. The dependent variable is defined as  $\Delta$ QTcF. The fixed effect parameters are intercept, and slope, and subject was included as a random effect on both intercept and slope terms.

Based on the output of the model, the slope estimate (95% CI) for niraparib concentration- $\Delta$ QTcF relationship was 1.41 (-3.17, 6.00) ms/( $\mu$ g/mL) and it was not statistically significant ( $p=0.55$ ). Observed and model estimated  $\Delta$ QTcF versus the observed niraparib concentrations are visualized in Figure 6. The geometric mean  $C_{\max}$  value on Cycle 1 Day 1 with a single dose of 300 mg niraparib was 588 ng/mL, with  $T_{\max}$  being at 3-4 h. The predicted upper bound of 90% CI for the  $\Delta$ QTcF response at this therapeutic  $C_{\max}$  was 4.78 ms (<10 ms). As stated earlier, the steady state  $C_{\max}$  after multiple dosing is expected to be  $\sim 1.8$ -fold higher than the  $C_{\max}$  after a single dose, so the exposures from Day 1 after single dose were not considered adequate to characterize QTc effects.

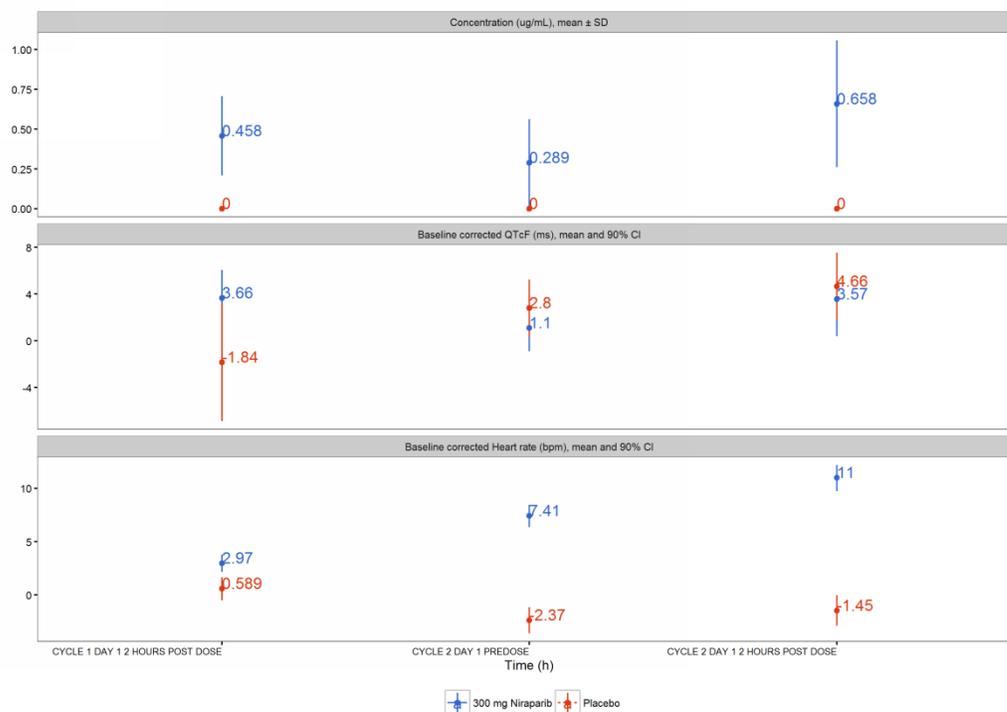
**Figure 6: Observed and Estimated  $\Delta$ QTcF vs. Drug concentration. The points and bars represent  $\Delta$ QTcF mean and 90% CI at the median concentration in a bin. Black line represents predictions from the concentration- $\Delta$ QTcF model. The shaded area represents the 90% CI of the prediction.**



### Assessment with data from NOVA Main Study

In order to evaluate QTc effects at steady state, the data from all patients in NOVA Main Study were evaluated because in these patients, ECG/PK was collected at pre-dose and 2 h post-dose on Cycle 2 Day 1 apart from 2 h post-dose on Cycle 1 Day 1, after continuous 300 mg QD dosing. Figure 7 shows the comparison of drug concentration,  $\Delta$ QTcF and  $\Delta$ HR for each of the sampling time points.

**Figure 7: Drug concentration,  $\Delta$ QTcF, and  $\Delta$ HR for each of the sampling time points in NOVA Main Study. Error bars illustrate mean  $\pm$  SD for concentration and 90% CI for  $\Delta$ HR and  $\Delta$ QTcF**



From the data in QTc substudy, it was evident that 2 h does not represent the true  $T_{max}$  since concentrations at 3 and 4 h were higher than at 2 h and thus, it is likely that the assessment scheme of 2 h post-dose in Cycle 2 is not optimal to capture the  $C_{max}$ . The appropriate information about  $C_{max}$  can be borrowed from the food effect study, where the least square mean  $C_{max}$  concentration in the fasted state after single dose of 300 mg niraparib was 0.677  $\mu\text{g}/\text{mL}$ . With the expected accumulation by 1.79-fold with the multiple dosing, the  $C_{max}$  at steady state in the fasted state would be 1.212  $\mu\text{g}/\text{mL}$ . This information can be utilized for predicting the QTc response at the expected concentrations once the exposure-QTc relationship is established from the data in the NOVA Main Study.

For this analysis, data was modeled with a prespecified linear mixed effect model. The dependent variable is defined as  $\Delta$ QTcF. The fixed effect parameters are intercept, baseline QTc (difference between average baseline and individual baseline), slope (concentration), time (categorical), and treatment (active/placebo). Subject was included as a random effect on both intercept and slope terms.

The final fixed effect parameters for the model are listed in Table 18.

**Table 18: Niraparib concentration- $\Delta$ QTcF relationship fixed effects parameter estimates and their associated precision, based on Kenward-Roger approximation**

Fixed effect parameter	Estimate	Lower 95% CI	Upper 95% CI	RSE (%)	p-value
(Intercept)	1.18	-2.28	4.64	149.07	0.503
TIME: CYCLE 2 DAY 1 2 HOURS POST DOSE	1.80	-1.41	5.02	90.86	0.272
TIME: CYCLE 2 DAY 1 PREDOSE	0.81	-2.36	3.98	198.40	0.615
ACTIVE1	-0.81	-5.41	3.78	-288.30	0.73
I(QTCF.BS - QTCF.mB)	-0.16	-0.22	-0.11	-16.67	<0.001
CONC	3.82	-2.03	9.68	77.73	0.205

Based on the output, niraparib concentration-  $\Delta$ QTcF relationship was not statistically significant, with the slope estimate being 3.82 (95% CI: [-2.03; 9.68]) ms/( $\mu$ g/ml) (p-value=0.205).

To rule out a clinically significant effect on QTc, we need to estimate the  $\Delta\Delta$ QTcF at  $C_{max}$ .  $\Delta\Delta$ QTcF is defined as the model-derived difference between  $\Delta$ QTcF at concentration of interest and model-derived  $\Delta$ QTcF for placebo at concentration 0, (ACTIVE=0).

Table 19 below shows  $\Delta$ QTcF and  $\Delta\Delta$ QTcF estimates at the steady state  $C_{max}$  of 1.212  $\mu$ g/mL for the tested dose of 300 mg QD. The predicted upper bound of 90% CI for the response at this  $C_{max}$  was 9.97 ms and 8.67 ms respectively for  $\Delta$ QTcF and  $\Delta\Delta$ QTcF.

**Table 19: Niraparib  $\Delta$ QTcF and  $\Delta\Delta$ QTcF estimates at the steady state mean  $C_{max}$  for the therapeutic dosing of 300 mg QD**

Exposure	Parameter	Concentration ( $\mu$ g/ml)	Estimate	Lower 90% CI	Upper 90% CI
Steady State	$\Delta$ QTcF	1.212	5.8	1.63	9.97
Mean Cmax	$\Delta\Delta$ QTcF	1.212	3.82	-1.03	8.67

Model performance was assessed by plotting observed and model estimated  $\Delta$ QTcF versus the observed niraparib concentrations in Figure 8.

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**Figure 8: Goodness of fit showing observed and estimated  $\Delta QTcF$  vs. drug concentrations. The points and bars represent  $\Delta QTcF$  mean and 90% CI at the median concentration in a bin. Black line represents predictions from the prespecified Concentration- $\Delta QTcF$  model. The shaded area represents the 90% CI of the prediction.**

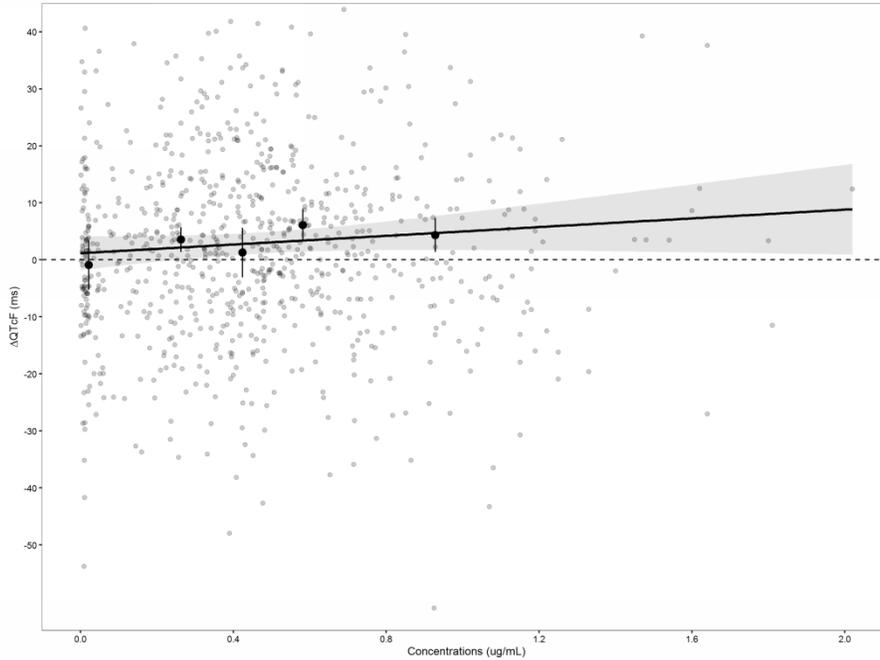
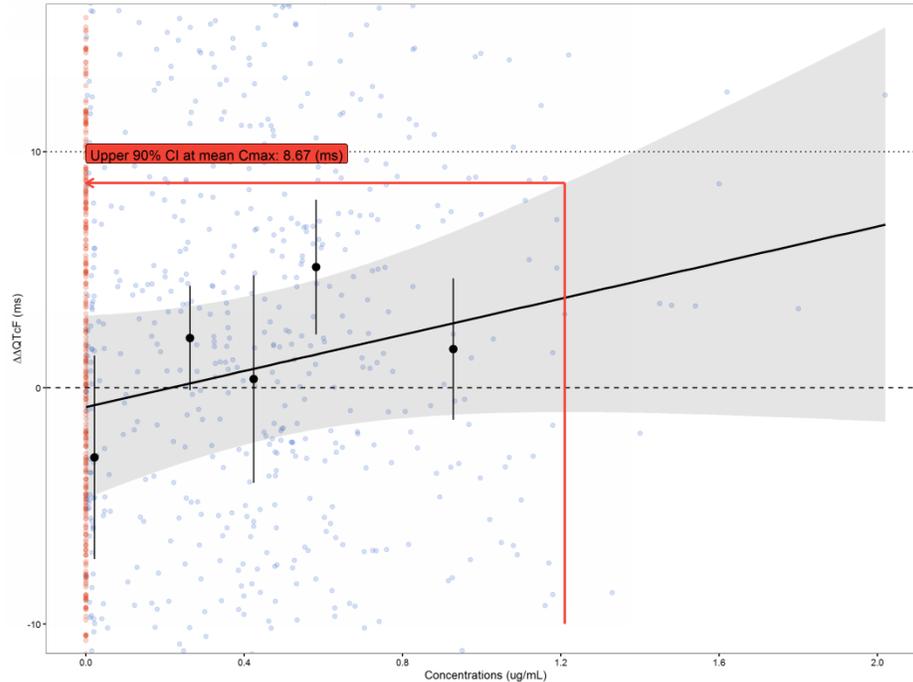


Figure 9 illustrates the relationship between  $\Delta\Delta QTcF$  and plasma concentrations of niraparib. The observed data in the figure is calculated arithmetically and represented along with model derived  $\Delta\Delta QTcF$  and the concentration- $\Delta\Delta QTcF$  relationship. The figure shows the predicted upper bound of 90% CI for  $\Delta\Delta QTcF$  at the expected steady state  $C_{max}$  (1.212  $\mu\text{g/mL}$ ) for the studied dosing regimen of 300 mg QD of niraparib in the study.

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**Figure 9: Prediction plots showing observed and estimated  $\Delta\Delta\text{QTcF}$  versus drug concentrations. The figure shows observed  $\Delta\Delta\text{QTcF}$  as scatter points and bins. The points and bars represent  $\Delta\Delta\text{QTcF}$  mean and 90% CI at the median concentration in a bin. The black line represents predictions from the concentration- $\text{QTcF}$  model prespecified by the reviewer. The shaded area represent the 90% CI of the prediction. The figure also shows model estimated  $\Delta\Delta\text{QTcF}$ . Arrow indicates the  $\Delta\Delta\text{QTcF}$  upper 90% CI at geometric mean  $C_{\text{max}}$  for the therapeutic dose studied.**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines, i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

No clinically meaningful effects of niraparib on the PR and QRS intervals were detected.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	300 mg QD	
Maximum tolerated dose	300 mg QD	
Principal adverse events	<p>The most common drug related AEs were nausea (270 patients [73.6%]), anemia (178 patients [48.5%]), thrombocytopenia (169 patients [46.0%]), fatigue (168 patients [45.8%]), constipation (146 patients [39.8%]), vomiting (126 patients [34.3%]), headache (95 patients [25.9%]), decreased appetite (93 patients [25.3%]), insomnia (89 patients [24.3%]) and platelet count decreased (74 patients [20.2%]).</p> <p>The most commonly reported Grade 3-4 drug related AEs were thrombocytopenia (104 patients [28.3%]), anemia (91 patients [24.8%]), platelet count decreased (27 patients [7.4%]), fatigue (21 patients [5.7%]), nausea (11 patients [3.0%]), vomiting (7 patients [1.9%]), constipation (2 patients [0.5%]), decreased appetite (1 patient [0.3%]), headache (1 patient [0.3%]) and insomnia (1 patient [0.3%]).</p> <p>The dose limiting toxicity of this compound is thrombocytopenia.</p>	
Maximum dose tested	Single Dose	400 mg
	Multiple Dose	400 mg QD, Cycle (defined as 21 days of dosing)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) $C_{max}$ : 2121.55 ± 552.76 nM and $AUC_{0-24}$ : 26581.46 ± 5494.01 (hr*nM)
	Multiple Dose	Mean (%CV) $C_{max}$ : 4448.42 ± 990.00 nM and $AUC_{0-24}$ : 79055.48 ± 20899.21 (hr*nM)
Range of linear PK	30 mg to 400 mg	
Accumulation at steady state	Geometric mean accumulation ratios following a QD 300-mg QD dose were 2.41 (1.70, 5.34), 1.79 (1.13, 3.97) for $AUC_{0-24}$ and $C_{max}$ , respectively; and were consistent across dose levels on a QD regimen.	
Metabolites	Niraparib is metabolized primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1. In a mass balance study (N=6), M1 and the subsequently formed M1 glucuronides (M10 and its isomers) were the major circulating metabolites. The mean half-life of M1 was 88	

	<p>hours. The exposure ratio of M1 to niraparib was approximately 1.3-2.2 folds in plasma. Based on the [<sup>14</sup>C]-radioactivity, the glucuronide metabolites (M10 and its isomers), collectively, represent approximately 55.7% of the AUC of total radioactivity, M1 9.3%, niraparib 2.4%, and a minor methylated M1 2.5%.</p>	
Absorption	Absolute/Relative Bioavailability	The oral bioavailability of the compound in cancer patients were approximately 73%
	T <sub>max</sub>	Median (range) for parent: By inspection of the data on Day 1 at the highest dose of 400 mg tested in humans plasma concentrations rise to peak levels over approximately 3.5 [1.5, 6.0] hrs, and is consistent with estimates across dose levels. Similarly, following the administration of the recommended therapeutic dose (300 mg), the median of T <sub>max</sub> was approximately in 2-4 hrs. Median T <sub>max</sub> for the major primary metabolite M1 is 6 and 9 hrs.
Distribution	Vd/F or Vd	The apparent volume of distribution (Vd/F) was 1220 L, indicating extensive tissue distribution of niraparib. In a population pharmacokinetic analysis, the Vd/F of niraparib was 1074 L in cancer patients.
	% bound	Moderately bound to plasma proteins in rats, dogs, and humans. The mean values for the unbound fraction (expressed as percent) in rat, dog, and human plasma were 16%, 28%, and 17%, respectively.
Elimination	Route	Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following administration of a single oral 300-mg dose of [ <sup>14</sup> C]-niraparib, on average 86.2% (range 71% to 91%) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the feces for 38.8% (range 28.3% to 47.0%) of the dose. In pooled samples collected over 6 days, 36.7% of the dose was recovered in the urine primarily as metabolites and 21.1% of the dose was recovered in the feces

		primarily as unchanged niraparib.
	Terminal $t_{1/2}$	Following a single oral 300-mg dose of niraparib, the mean terminal half-life ( $t_{1/2}$ ) of niraparib ranged from 48 to 51 hours (approximately 2 days).
	CL/F or CL	In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.
Intrinsic Factors	Age	Population pharmacokinetic analyses indicated that age had no significant impact on the pharmacokinetics of niraparib.
	Sex	Population pharmacokinetic analyses indicated that gender had no significant impact on the pharmacokinetics of niraparib.
	Race	Population pharmacokinetic analyses indicated that race had no significant impact on the pharmacokinetics of niraparib.
	Hepatic & Renal Impairment	Based on the population PK analysis, baseline serum albumin, AST, total bilirubin, and ALT levels did not have a clinically important effect on niraparib pharmacokinetics in patients with mild and moderate of hepatic impairment. Based on the population PK analysis, creatinine clearance in the range of 29 to 150 mL/min had no significant impact on the pharmacokinetics of niraparib in patient with mild and moderate renal impairment. The effect of severe hepatic and renal impairment on niraparib pharmacokinetics was not studied.
Extrinsic Factors	Drug interactions	Clinical drug-drug interaction (DDI) studies for niraparib have not been conducted. A series of in vitro DDI studies, particularly the interactions with cytochromes P450 (CYPs) and transporters, were carried out and the results from these studies unambiguously showed the minimal potential for DDI in the clinic. Consistent with mainly non-CYP-catalyzed metabolism determined in

		<p>in vitro, the human AME study carried out further demonstrated the lack of the involvement of cytochromes P450 (CYPs) in niraparib metabolism. The minor oxidative metabolites formed by CYPs (CYP1A2 and CYP3A4) in vitro were indeed undetectable in the circulation of any patient studied. Therefore, modulation (inhibition and/or induction) of drug-metabolizing CYPs, namely CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, by the potential concomitant agents would not affect the hepatic clearance, thus the exposure of niraparib in humans. Likewise, niraparib and the major primary metabolite M1 are neither inhibitory against any drug-metabolizing CYPs, nor inductive towards CYP3A4. Therefore, neither niraparib nor the major primary metabolite bear the potential risk of acting as perpetrators when administered concurrently with other therapeutic agents, including anticancer agents, which are the substrates of CYPs. Niraparib was determined to be a substrate of P-gp and a substrate/inhibitor of breast cancer resistance protein (BCRP) with modest potency. However, neither niraparib nor the major primary metabolite M1 was shown to be interactive with any of the major hepatic and renal uptake transporters, namely organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). More importantly, neither niraparib nor M1 elicited any potential to interact with bile salt export pump (BESP), an efflux transporter known to be associated with hepatotoxicity.</p>
	Food Effects	<p>Concomitant administration of a high fat meal did not significantly affect the pharmacokinetics of niraparib after administration of 300 mg of niraparib.</p>

Expected High Clinical Exposure Scenario	The supra-therapeutic dose has not been determined. The highest dose tested to date is 400 mg QD.
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/s/  
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DHANANJAY D MARATHE

02/14/2017

Xiaofeng Wang was the Primary Reviewer.

XIAOFENG WANG

02/14/2017

DALONG HUANG

02/14/2017

QIANYU DANG

02/14/2017

MICHAEL Y LI

02/14/2017

CHRISTINE E GARNETT

02/14/2017

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### **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\*\*\***

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<b>Date of This Review:</b>	January 12, 2017
<b>Requesting Office or Division:</b>	Division of Oncology Products 1 (DOP1)
<b>Application Type and Number:</b>	NDA 208447
<b>Product Name and Strength:</b>	Zejula (niraparib) capsules, 100 mg
<b>Product Type:</b>	Single ingredient product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Tesaro, Inc.
<b>Submission Date:</b>	October 31, 2016 and January 6, 2017
<b>OSE RCM #:</b>	2016-2454
<b>DMEPA Primary Reviewer:</b>	Tingting Gao, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

Tesaro, Inc. submitted the proposed container label and prescribing information (PI) for Zejula (niraparib) capsules for NDA 208447. This is a New Molecular Entity (NME) product with a proposed indication for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

The Division of Oncology Products 1 (DOP1) requested that we review the submitted Zejula container label 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.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
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 evaluated the proposed Zejula container labels, and noted the followings:

- The strength statement is located above the proprietary name, which is not presented in an order that US healthcare professionals are accustomed to.
- The “( (b) (4) )” statement after the net quantity statement is misleading since the bottle of 90 capsules may provide more than (b) (4) supply if the dose is modified to 200 mg per day or 100 mg per day
- The “ (b) (4) ” statement is unnecessary since it is not required per 21 CFR (b) (4) products. We recommend remove this statement to reduce information crowding on the principal display panel.
- We recommend deleting or moving the statement “REV. XX/XX” to the side panel as the principal display panel should include critical information to ensure safe product use.
- The format of the expiration date is currently presented as “ (b) (4) ” which may lead to misinterpretation of the expiration date as “MMDDYY”.

- As currently presented on the left side panel, it appears that there are two (b) (4) codes. We plan to clarify what information is included on the two (b) (4) codes.

We reviewed the proposed PI and recommend that the dose be presented as “300 mg (three 100 mg capsules)” to indicate that three capsules is required to construct the dose of 300 mg to minimize the risk of wrong dose errors. We also noticed that instruction to swallow each capsule whole was not included in Section 2.1 Recommended Dosage in the PI. Lastly, we recommend revising the statement “#00 mg/day” in Table 1 to “#00 mg/day ([three/two/one] 100 mg capsules)” for clarity and to prevent misinterpretation and confusion.

#### 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and PI for Zejula may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

###### A. Prescribing Information

###### a. Dosage and Administration Section

- Revise the statement “The recommended dose of ZEJULA as monotherapy is (b) (4) taken orally once daily (b) (4) to “The recommended dose of ZEJULA is monotherapy is 300 mg (three 100 mg capsules) taken orally once daily” for clarity.
- In Section 17 Patient Counseling Information, it states “Each capsule should be swallowed whole. Zejula may be taken with or without food.” We recommend include this important information in Section 2.1 Recommended Dosage.
- Revise the statement “#00 mg/day” in Table 1 to “#00 mg ([three/two/one] 100 mg capsules) per day” for clarity and to minimize the risk of misinterpretation and confusion.

##### 4.2 RECOMMENDATIONS FOR TESARO, INC.

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

###### A. Container label

1. Consider relocating the strength statement “100 mg” to immediately below the dosage form statement so the order of drug information presented is the proprietary name, established name, dosage form, and then the strength. As currently presented, the strength statement is located above the proprietary name, which is not presented in an order that US healthcare professionals are accustomed to. While the proposed Zejula is currently proposed as a single strength product so the risk of wrong strength selection error due to healthcare

professionals inadvertently overlooking the strength statement is not of a concern now, we encourage you to consider relocating the strength statement to after the dosage form in case future product development involves a different strength.

2. Remove the “(b)(4)” statement after the net quantity statement since the bottle of 90 capsules may provide more than (b)(4) supply if the dose is modified to 200 mg per day or 100 mg per day.
3. Remove the “(b)(4)” statement since it is not required per 21 CFR (b)(4) products and to reduce information crowding on the principal display panel.
4. Consider deleting or moving the statement “REV. XX/XX” to the side panel as the principal display panel should include critical information to ensure safe product use.
5. The format of the expiration date is currently presented as “(b)(4)”, which is not a date format that U.S. healthcare professionals and consumers are accustomed to so YY could be confused as the month, MM confused as the date, and DD confused as the year. Change the format of the expiration date to MMDDYYYY (if using all numbers) or MMMDDYYYY (if spelling out first three letters of the month) to minimize the risk of confusion.
6. As currently presented on the left side panel, it appears that there are two QR codes. Please clarify what the two (b)(4) codes are for, and what information is contained in the two (b)(4) codes.

APPEARS THIS WAY ON ORIGINAL

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Zejula that Tesaro, Inc. submitted on October 31, 2016.

<b>Table 2. Relevant Product Information for Zejula</b>											
<b>Initial Approval Date</b>	N/A										
<b>Active Ingredient</b>	niraparib										
<b>Indication</b>	for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy										
<b>Route of Administration</b>	oral										
<b>Dosage Form</b>	capsules										
<b>Strength</b>	100 mg										
<b>Dose and Frequency</b>	<p>The recommended dose of ZEJULA as monotherapy is three 100 mg capsules taken orally once daily, equivalent to a total daily dose of 300 mg.</p> <p>Dose modifications for adverse reactions</p> <table border="1"> <thead> <tr> <th colspan="2"><b>Table 1: Recommended dose modifications for adverse reactions</b></th> </tr> <tr> <th><b>Dose level</b></th> <th><b>Dose</b></th> </tr> </thead> <tbody> <tr> <td>Starting dose</td> <td>300 mg/day</td> </tr> <tr> <td>First dose reduction</td> <td>200 mg/day</td> </tr> <tr> <td>Second dose reduction</td> <td>100 mg/day*</td> </tr> </tbody> </table> <p>*If further dose reduction below 100 mg/day is required, discontinue ZEJULA.</p>	<b>Table 1: Recommended dose modifications for adverse reactions</b>		<b>Dose level</b>	<b>Dose</b>	Starting dose	300 mg/day	First dose reduction	200 mg/day	Second dose reduction	100 mg/day*
<b>Table 1: Recommended dose modifications for adverse reactions</b>											
<b>Dose level</b>	<b>Dose</b>										
Starting dose	300 mg/day										
First dose reduction	200 mg/day										
Second dose reduction	100 mg/day*										
<b>How Supplied</b>	90-count bottles										
<b>Storage</b>	Store at 20° to 25°C (68° to 77°F)										
<b>Container Closure</b>	The primary packaging configuration for niraparib 100 mg capsules is a 90-count, 175-cc, high-density polyethylene white bottle (b) (4) cap										

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>a</sup> along with postmarket medication error data, we reviewed the following Zejula label and labeling submitted by Tesaro, Inc. on October 31, 2016.

- Container label submitted on October 31, 2016
- Prescribing Information submitted on January 6, 2017

### **G.2 Label and Labeling Images**

#### **Container label**



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<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TINGTING N GAO  
01/12/2017

CHI-MING TU  
01/12/2017

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

**Application:** NDA 208447

**Application Type:** 505(b)(1)

**Drug Name(s)/Dosage Form(s):** Zejula™ (niraparib) Capsules

**Applicant:** TESARO, Inc.

**Receipt Date:** October 31, 2016

**PDUFA Date:** June 30, 2017

**Goal Date:** March 31, 2016

### 1. Regulatory History and Applicant's Main Proposals

TESARO submitted NDA 208447, for Zejula™ (niraparib), as a 505(b)(1) application on October 31, 2016. NDA 208447 references IND 100996.

The proposed indication for Zejula™ is:

Zejula™ is a poly(ADP-ribose) polymerase (PARP) (b)(4) inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

Zejula™ (niraparib) is designated as an NME with Breakthrough Therapy Designation, Fast Track Designation, and Orphan Designation.

The following table lists key regulatory meetings and regulatory correspondence with the Applicant:

Meeting Type or Correspondence	Meeting Date or Correspondence Date
Grant Orphan Designation	4/30/2010
End-of-Phase 2 Meeting	2/13/13
Deny Breakthrough Therapy Designation	7/26/13
CMC End-of-Phase 2 Meeting	2/17/15
Written Guidance on NDA application	3/20/15
Written Guidance on NDA application	3/25/15
Type C Guidance meeting	3/30/15
Type C Guidance meeting (WRO)	7/14/16
Grant Fast Track Designation and Rolling Review	9/7/16
Pre-NDA meeting	9/21/16
Grant Breakthrough Therapy Designation	10/14/16

# RPM PLR Format Review of the Prescribing Information

## 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

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. Revise all headings in the HIGHLIGHTS section so that the headings are presented in the center of a horizontal line.
2. Revise PATIENT COUNSELING INFORMATION reference statement to read, "Advise the patient to read the FDA-approved patient labeling (Patient Information)".

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 January 6, 2016. The resubmitted PI will be used for further labeling review.

APPEARS THIS WAY ON ORIGINAL

# Selected Requirements of Prescribing Information

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

- YES** 3. 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:** N/A

- YES** 4. 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:** N/A

- YES** 5. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:** N/A

- NO** 6. 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:** Not all headings are presented in the center of the horizontal line.

- YES** 7. 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** 8. 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** 9. Headings in HL must be presented in the following order:

Heading	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required

## Selected Requirements of Prescribing Information

• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	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** 10. 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

- YES** 11. 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:*

#### Product Title in Highlights

- YES** 12. Product title must be **bolded**.

*Comment:*

#### Initial U.S. Approval in Highlights

- NO** 13. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

*Comment:* *Currently the year reads: YYYY. To be revised upon approval.*

#### Boxed Warning (BW) in Highlights

- N/A** 14. All text in the BW must be **bolded**.

*Comment:*

- N/A** 15. 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**

## Selected Requirements of Prescribing Information

16. 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 17. 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 18. 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:

- N/A 19. 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 20. 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:

### Dosage Forms and Strengths in Highlights

- N/A 21. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

### Contraindications in Highlights

- YES 22. 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 23. 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](http://www.fda.gov/medwatch).**”

Comment:

### Patient Counseling Information Statement in Highlights

YES

SRPI version 6: February 2016

Page 5 of 11

## Selected Requirements of Prescribing Information

24. 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

**NO**

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

*Comment:* *Currently date reads "M/201Y". To be revised upon approval.*

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## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 26. The TOC should be in a two-column format.  
*Comment:*
- YES** 27. 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** 28. 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** 29. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 30. 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** 31. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 32. 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:*

APPEARS THIS WAY ON ORIGINAL

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 33. 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.

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

**Comment:**

- YES** 34. 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** 35. 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** 36. 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** 37. All text in the BW should be **bolded**.

*Comment:*

- N/A** 38. 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** 39. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 40. 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:*

- N/A** 41. 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

- NO** 42. 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:** *Wording is correct. However, "Patient Information" is in all caps and needs to be corrected.*

- YES** 43. 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:**

APPEARS THIS WAY ON ORIGINAL

# 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](http://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.

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/s/  
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JEANNETTE L DININ  
12/16/2016

ALICE KACUBA  
12/16/2016

## 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 # 208447 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Zejula™ Established/Proper Name: niraparib Dosage Form: Capsules Strengths: 100 mg Route(s) of Administration: Oral		
Applicant: TESARO, Inc. Agent for Applicant (if applicable):		
Date of Application: October 31, 2016 Date of Receipt: October 31, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: June 30, 2017		Action Goal Date (if different): March 31, 2017
Filing Date: December 30, 2016		Date of Filing Meeting: December 14, 2016
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): The maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		

Type of BLA  <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)			
Review Classification:  <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <li>• <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)</i></li> <li>• <i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li>• <i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li>• <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher			
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division <i>(if OTC product)</i> :				
List referenced IND Number(s): IND 100996				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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 to the supporting IND(s) if not already entered into electronic archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		Not Applicable
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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 <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> 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:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> 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: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a></i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>  <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes</b> , answer the bulleted questions below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> <li>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)].</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><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></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 20%;">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																	
<p><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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 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></p>																				
<ul style="list-style-type: none"> <li>If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If no, include template language in the 74-day letter.</b></p> <p><b>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</b></p> <p><i>Note: <b>Pharmaceutical equivalents</b> are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; <b>and</b> (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		

<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>NDA/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes, # years requested:</b> 5 years  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>NDA only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

APPEARS THIS WAY ON ORIGINAL

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no</b>, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?   <b>If yes</b>, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included.</i>  <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?   <b>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</b></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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, both 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&amp;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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Application has Orphan Designation. Orphan Designation number: 10-3065
<p><b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b><u>BPCA:</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

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<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> 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?	<input checked="" type="checkbox"/>  <input checked="" type="checkbox"/>	<input type="checkbox"/>  <input type="checkbox"/>	<input type="checkbox"/>  <input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> <b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent 11/3/16
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent 11/3/16
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent 11/3/16
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH Sent 11/3/16 IRT/QT Sent 11/3/16
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 2/13/13, 2/17/15	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 9/21/16	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 14, 2016

**BACKGROUND:**

TESARO submitted NDA 208447, for Zejula™ (niraparib), as a 505(b)(1) application on October 31, 2016. NDA 208447 references IND 100996.

The proposed indication for Zejula™ is:

Zejula™ is a poly(ADP-ribose) polymerase (PARP) (b)(4) inhibitor indicated for the maintenance treatment of adult patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

The indication will be a review issue. Zejula™ (niraparib) is currently designated as an NME with Breakthrough Therapy Designation, Fast Track Designation, and Orphan Designation.

The following table lists key regulatory meetings and regulatory correspondence with the Applicant:

<b>Meeting Type or Correspondence</b>	<b>Meeting Date or Correspondence Date</b>
Grant Orphan Designation	4/30/2010
End-of-Phase 2 Meeting	2/13/13
Deny Breakthrough Therapy Designation	7/26/13
CMC End-of-Phase 2 Meeting	2/17/15
Written Guidance on NDA application	3/20/15
Written Guidance on NDA application	3/25/15
Type C Guidance meeting	3/30/15
Type C Guidance meeting (WRO)	7/14/16
Grant Fast Track Designation and Rolling Review	9/7/16
Pre-NDA meeting	9/21/16
Grant Breakthrough Therapy Designation	10/14/16

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Jeannette Dinin	Y
	CPMS/TL:	Alice Kacuba	Y
Cross-Discipline Team Leader (CDTL)	Laleh Amiri-Kordestani		N
Division Director/Deputy	Geoffrey Kim – Director		Y
	Amna Ibrahim – Deputy Director		N

	Julia Beaver – Associate Director	N
Office Director/Deputy	Richard Pazdur	N
Clinical	Reviewer: Gwynn Ison	Y
	TL: Laleh Amiri-Kordestani	N
Clinical Pharmacology	Reviewer: Vadryn Pierre	Y
	TL: Pengfei Song	Y
• Genomics	Reviewer: Anuradha Ramamoorthy	
	TL: Rosane Charlab Orbach	
• Pharmacometrics	Reviewer: Fang Li	
	TL: Jingyu (Jerry) Lu	
• IRT/QT	Reviewer: Devi Kozeli	
Biostatistics	Reviewer: Lijun Zhang	Y
	TL: Shenghui Tang	Y

Nonclinical Pharmacology/Toxicology)	Reviewer: Wimolnut Manheng	Y
	TL: Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer: N/A	N/A
	TL: N/A	N/A
Product Quality (CMC) Review Team:	ATL: Xiao Hong Chen	Y
	RBPM: Kristine Leahy	N
• Drug Substance	Reviewer: Sharon Kelly	N
• Drug Product	Reviewer: William (Mike) Adams	Y
• Process	Reviewer: Kumar Janoria	N
	Mautang Zhou	N
• Microbiology	Reviewer: Kumar Janoria	N
	Mautang Zhou	N
• Facility	Reviewer: Viviana Matta	Y
• Biopharmaceutics	Reviewer: Dave Kaushalkumar	Y
	TL: Okpo Eradiri	Y
• Immunogenicity	Reviewer: N/A	N/A
• Labeling (BLAs only)	Reviewer: N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	Brach Chief: Anamitro Banerjee	N
	EA: Raanan Bloom	N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer: Morgan Walker	Y
	TL: Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container	Reviewer: Kevin Wright	N

labeling)	TL:	Trung-Hieu (Brian) Tran	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	N
	TL:	Alice (Chi-Ming) Tu	N
OSE/DRISK (REMS)	Reviewer:	Elizabeth Everhart	Y
	TL:	Naomi Redd	N
Division of Epidemiology (DEPI)	Reviewer:	Steven Bird	N
	TL:	Caroly McCloskey	N
Pharmacovigilance (DPV)	Reviewer:	Pritpal Singh	Y
	TL:	Afrouz Nayernama	N
OSE RPM	Reviewer:	Frances Fahnbulleh	Y
	TL:	Sue Kang	N

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines			
Safety	Reviewer:	Michael Brave	Y
	RPM:	Christina Marshall	N
	TL:	Katherine Fedenko	Y
Other attendees	William Pierce (Labeling)		Y
	Fang Li		Y
	Lynn Howie		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues:             <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>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):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> No comments</p>

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public</i></li> </ul>	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason: The application did not raise significant safety or efficacy issues</p>

<p><i>health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></p>	
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>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?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES - submitted 11/23/16 <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	None
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

APPEARS THIS WAY ON ORIGINAL

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Richard Pazdur, MD

**Date of Mid-Cycle Meeting:** 2/6/17

**21<sup>st</sup> Century Review Milestones:**

**PDUFA DATE:** 6/30/17

**GOAL DATE:** 3/31/17

MidCycle: 2/6/17

Internal Late cycle: 3/2/17

Late cycle: 3/7/17

**Labeling meetings**

2 1/17: CMC/DMEPA

2 8/17: Non-Clinical

2 10/17: Clinical/Stats

2 13/17: Clinical/Stats

2 15/17: Clinical/Stats

2 22/17: Clinical Pharmacology (requested)

7<sup>th</sup> meeting to be scheduled for after Sponsor return discussion

**Reviews due:**

Primary reviews due: 3/3/17

Secondary review due: 3/7/17

CDTL memo: 3/10/17 – may change some as no need for 21 days between CDTL memo and sign off, however dependent on CDRH timeline for complimentary diagnostic

Action package to Division director: 3/21/17

Sign off by Pazdur: 3/31/17

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

<b>ACTION ITEMS</b>	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	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.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

**APPEARS THIS WAY ON ORIGINAL**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEANNETTE L DININ  
12/16/2016

ALICE KACUBA  
12/16/2016