

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208447Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208447

SUPPL #

HFD #

Trade Name Zejula

Generic Name niraparib

Applicant Name TESARO, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity? YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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d) Has pediatric exclusivity been granted for this Active Moiety? YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade? YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support

the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

/s/

JEANNETTE L DININ
03/27/2017

GEOFFREY S KIM
03/27/2017

1.3. Administrative Information

3. DEBARMENT CERTIFICATION

TESARO, Inc. 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.



Chuck Miller
Vice President, Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208447 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zejula™ Established/Proper Name: niraparib Dosage Form: Capsules		Applicant: TESARO, Inc. Agent for Applicant (if applicable):
RPM: Jeannette Dinin		Division: Oncology Products 1
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity. <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is 6/30/17 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|--|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: ACSO Burst, OCP Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): Approval 3/27/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included: 3/21/17
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included: 10/31/17
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included: 3/22/17
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included: 10/31/17
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included: 2/8/17
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	12/16/16
• Review(s) <i>(indicate date(s))</i>	12/9/16
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 12/16/16 DMEPA: 1/12/17, 2/15/17 DMPP/PLT (DRISK): 3/10/17 OPDP: 3/9/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality 3/2/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	12/16/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed 3/17/17
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No checked 12/8/16 and 3/20/17
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo <i>(indicate date)</i>	
○ If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	<input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>3/15/17: For fallopian tube and primary peritoneal indications</u> If PeRC review not necessary, explain: <u>Not applicable for ovarian cancer indication— ovarian cancer indication has orphan designation</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	October 14, 2016
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	Included
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <u>MPC SharePoint Site</u></i>)</p>	Not completed
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	3/21/17 (x2), 3/14/17, 3/9/17, 3/2/17, 2/28/17 (x2), 2/27/17, 2/23/17, 2/21/17, 2/9/17 (x2), 2/3/17, 2/2/17, 2/1/17, 1/31/17, 1/27/17, 1/26/17, 1/25/17 (x3), 1/24/17, 1/18/17, 1/10/17, 1/3/17, 12/20/16, 12/19/16, 12/16/16 (x2), 12/15/16 (x2), 12/12/16 (x3), 12/5/16, 12/1/16, 11/30/16, 11/18/16, 11/16/16, 11/14/16, 11/8/16, 10/17/16,
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	MPC meeting minutes: 9/29/16
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/21/16
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 2/13/13
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 2/10/17
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 3/7/17
<ul style="list-style-type: none"> • Other milestone meetings <ul style="list-style-type: none"> CMC EOP2 meeting Written Guidance Written Guidance Guidance Guidance (WRO) 	2/17/15 3/20/15 3/25/15 3/30/15 7/14/16

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None Signed multi-disciplinary review 3/24/17
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Signed multi-disciplinary review 3/24/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None signed executive summary portion of multi-disciplinary review 3/22/17
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1 PMR, 4 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Signed Clinical/Stats portion of multi-disciplinary review 3/22/17
• Clinical review(s) (<i>indicate date for each review</i>)	Signed Clinical/Stats portion of multi-disciplinary review 3/22/17 Filing Review: 12/14/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Completed in section 11.9 of Signed Clinical/Stats portion of multi-disciplinary review (page 11-92)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input type="checkbox"/> None CDRH: 3/16/17 QT/IRT: 2/14/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	N/A N/A <input type="checkbox"/> None 3/7/17 – Primary Review; 3/8/17 – Team Leader sign off
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 2/28/17

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review Signed Clinical/Stats portion of multi-disciplinary review 3/22/17
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review Signed Clinical/Stats portion of multi-disciplinary review 3/22/17 Signed Filing Review: 12/16/16
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Signed Clinical/Stats portion of multi-disciplinary review 3/22/17 Filing Review: 12/16/16
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review; Signed Clinical Pharmacology portion of multi-disciplinary 3/16/17
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review Signed Clinical Pharmacology portion of multi-disciplinary 3/16/17 Signed Filing Review: 12/15/16
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Signed Clinical Pharmacology portion of multi-disciplinary 3/16/17 Filing Review: 12/15/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review - Signed Non-Clinical/Toxicology portion of multi-disciplinary 3/13/17
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review - Signed Non-Clinical/Toxicology portion of multi-disciplinary 3/13/17 Signed Filing Review: 12/12/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Non-Clinical/Toxicology portion of multi-disciplinary 3/13/17 Filing Review: 12/12/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Drug Substance: Signed Primary review 2/24/17 Drug Product: Signed Primary review 3/2/17 Process: Signed Primary review 3/1/17 Biopharmaceutics: Signed Primary review 2/21/17
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Executive Summary: 3/9/17 Drug Substance: 2/22/17 Drug Product: 3/2/17 Filing Review: 12/16/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None Process: 2/28/17 Biopharmaceutics: 2/21/17 Method Verification: 2/10/17
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Primary review 2/24/17 TL signed Primary review: 2/24/17
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable: 2/21/17 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
<ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/Zejula/IR - device
Date: Tuesday, March 21, 2017 2:15:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following: You provided a response to a CDRH request on CDx interaction, to NDA 208447, Sequence 0040. Please let us know if you agree to Myriad including (b) (4) in the device labeling.

Please respond by **12:00 pm, Thursday, March 23, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
03/21/2017

From: Dinin, Jeannette
To: [Chuck Miller](#)
Subject: NDA 208447/Zejula/Label_3/21/17 - Time sensitive
Date: Tuesday, March 21, 2017 10:36:00 AM
Attachments: NDA 208447_draft-labeling-redline_3-21-17.docx
image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request concurrence of the attached label. Please review, accept changes/edit and send back by no later than **12:00 pm, tomorrow, March 22, 2017.**

Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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JEANNETTE L DININ
03/21/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA communication: NDA 208447/Zejula/label
Date: Tuesday, March 14, 2017 1:38:00 PM
Attachments: image001.png
ZEJULA PPI - marked copy.docx
NDA 208447-Label-3-14-17.docx
Importance: High

Dear Mr. Miller,

The purpose of this email is to convey additional changes to the package insert and patient package insert (PPI) for NDA 208447 labeling. Note, please use the attached PPI as your base to retain formatting changes. Please review and reply within two business days.

Please reply by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
03/14/2017

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/Zejula/Label
Date: Thursday, March 09, 2017 2:06:00 PM
Attachments: NDA 208447-Label _3-9-17 .docx
image001.png

Dear Mr. Miller,

The purpose of this email is to request review and response to the attached NDA 208447 label. Please note, not all reviews are completed so this label does not provide for final agreed upon language.

Please respond by 9:00 am, EST, Monday, March 13, 2017. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
03/09/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA communication: NDA 208447/Zejula/Label - redline version
Date: Tuesday, March 07, 2017 8:03:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request you re-submit the red-line version of the label, submitted on March 2, 2017. Upon review, It appears that some new text is not currently in track change form. Please review and re-submit, ensuring that all changes made after accepting FDA proposed wording is in track change form.

As a reminder, not all FDA reviews are finished, therefore this is not the agreed upon label and there may be additional changes.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
03/07/2017

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: 208447

PRODUCT PROPRIETARY NAME: Zejula

ESTABLISHED/GENERIC NAME: niraparib

APPLICANT/SPONSOR: TESARO, inc.

PREVIOUSLY APPROVED INDICATION/S: None

- (1) _____
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

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, (note - covered by Orphan designation) fallopian tube, (note - not covered by orphan designation) or primary peritoneal cancer (note – not covered by orphan designation) who are in response to platinum-based chemotherapy.

BLA/NDA STAMP DATE: 10/31/16

PDUFA GOAL DATE: 6/30/17

ACTION GOAL DATE: 3/31/17

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER: Not applicable

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen;* or *route of administration?*

Did the sponsor submit an Agreed iPSP? Yes No

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes No - not applicable

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes No

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

- 1 Pediatric age group(s) to be waived.
- 2 Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. *Provide justification for Waiver:* Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:* Not applicable

APPEARS THIS WAY ON ORIGINAL

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis	diabetic foot infections
acute bacterial exacerbations of chronic bronchitis (a complication of chronic obstructive pulmonary disease)	digestive disorders (gallstones)
adjunctive treatment of major depressive disorder	dry eye syndrome (keratoconjunctivitis sicca)
age-related macular degeneration	dupuytren's disease and manifestations
Alzheimer's disease	erectile dysfunction essential thrombocytosis
amyloidosis	giant cell arteritis
amyotrophic lateral sclerosis	gout
androgenic alopecia	Huntington's chorea
ankylosing spondylitis	idiopathic pulmonary fibrosis
atherosclerotic cardiovascular disease	infertility & reproductive technology
benign monoclonal gammopathy	juvenile psoriatic arthritis
benign prostatic hyperplasia	memory loss
cancer:	menopause and perimenopausal disorders
basal cell and squamous cell skin cancer	mesothelioma
bladder	microscopic polyangiitis
breast	myelodysplasia
cervical	myelofibrosis & myeloproliferative disorders
colorectal	opioid induced constipation in chronic, non-cancer pain
cholangiocarcinoma	osteoarthritis
endometrial	overactive bladder
esophageal	Parkinson's disease
fallopian tube	paroxysmal nocturnal hemoglobinuria
follicular lymphoma	plasma cells and antibody production disorders
gastric	polycythemia vera
hairy cell leukemia	polymyalgia rheumatica (PMR)
hepatocellular	postmenopausal osteoporosis
indolent non-Hodgkin lymphoma	prevention of stroke and systemic embolic events in atrial fibrillation
liposarcoma	psoriatic arthritis
lung (small & non-small cell)	reduction of thrombotic cardiovascular events in patients with coronary artery disease
multiple myeloma	replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
oropharynx (squamous cell)	retinal vein occlusions
ovarian (non-germ cell)	stress urinary incontinence
pancreatic	Sjogren's Syndrome
peritoneal	temporary improvement in the appearance of caudal lines
prostate	treatment of incompetent great saphenous veins and varicosities
refractory advanced melanoma	treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
renal cell	type 2 diabetic nephropathy
uterine	vascular dementia/vascular cognitive disorder/impairmen
chronic lymphocytic leukemia	
chronic obstructive pulmonary disease	
cryoglobulinemia	
diabetic peripheral neuropathy/macular edema	

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/s/

JEANNETTE L DININ
03/06/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: RE: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification
Date: Thursday, March 02, 2017 3:34:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

PMC #4 has been modified. Please see description below. Additionally, The analytical and clinical validation data may be submitted via (b) (4)

If you have any further questions please do not hesitate to ask. Please respond to the proposed PMC by 12:00 pm, EST, Monday, March 6, 2017.

PMC #4 Description: 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.

PMC Schedule Milestones: Final Report Submission: 12/2017

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



From: Chuck Miller [mailto:cmiller@tesarobio.com]
Sent: Tuesday, February 28, 2017 12:25 PM
To: Dinin, Jeannette

Subject: RE: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification

Hi Jeannette,

Thank you for the clarification. The other thing that our team is trying to understand is what exactly do

(b) (4)

Thanks so much for any clarity.

Best regards,

Chuck

Charles Miller
Vice President, Regulatory Affairs



TESARO, 1000 Winter St North, Waltham, MA 02451

Direct: +1 781.786.7026 | Mobile: (b) (6)

cmiller@tesarobio.com

www.tesarobio.com



From: Dinin, Jeannette [<mailto:Jeannette.Dinin@fda.hhs.gov>]

Sent: Tuesday, February 28, 2017 10:26 AM

To: Chuck Miller

Subject: RE: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification

Dear Mr. Miller,

We do not have additional milestone dates for either the CMC PMC's or the in-vitro diagnostic PMC. You may propose milestone dates if you feel further clarification would be helpful.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



From: Chuck Miller [<mailto:cmiller@tesarobio.com>]
Sent: Tuesday, February 28, 2017 9:59 AM
To: Dinin, Jeannette
Subject: RE: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification

Hi Jeannette,

Thank you for sending along!

Just to clarify a couple of items... for the CMC PMCs, do you need milestones other than the final submission date as noted? Also, for the in vitro diagnostic, (b) (4)

[Redacted text block]

Best regards,

Chuck

Charles Miller
Vice President, Regulatory Affairs



TESARO, 1000 Winter St North, Waltham, MA 02451

Direct: +1 781.786.7026 | Mobile: (b) (6)

cmiller@tesarobio.com

www.tesarobio.com



From: Dinin, Jeannette [<mailto:Jeannette.Dinin@fda.hhs.gov>]
Sent: Tuesday, February 28, 2017 6:06 AM
To: Chuck Miller
Subject: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification
Importance: High

Dear Mr. Miller,

The purpose of this email is to convey the following PMC's and PMR:

PMC #1 Description: 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 (b) (4) while still maintaining product quality and batch to batch consistency.

PMC #2 Description: Provide re-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 as drug release profiles with sampling at 5, 15, 30, 45 and 60 minutes. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

PMC #3 Description: Provide re-validation data for accuracy and precision using 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.

PMC (1-3) Schedule
Milestones:

Final Report Submission:

|

|

04/15/2018

PMC #4 Description: Submit to FDA the appropriate analytical and clinical validation data for the *in vitro* diagnostic assay that identifies homologous recombination deficiency (HRD) subset of epithelial ovarian, fallopian tube, or primary peritoneal cancer patients with a different therapeutic product effect for Niraparib.

PMC (#4) Schedule Milestones:

Final Report Submission:

12/2017

PMR Description: 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.

PMR Schedule Milestones:	Final Protocol Submission:	06/15/17
	Trial Completion:	11/15/18
	Final Study Report Submission:	02/15/19

Please review the content and dates of the PMC's and PMR. If you have any concerns regarding the content or due dates please respond by **12:00 pm EST, Thursday, March 2, 2017**.

Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
03/02/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/IR - PMC & PMR notification
Date: Tuesday, February 28, 2017 6:05:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to convey the following PMC's and PMR:

PMC #1 Description: 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 (b) (4) while still maintaining product quality and batch to batch consistency.

PMC #2 Description: Provide re-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 as drug release profiles with sampling at 5, 15, 30, 45 and 60 minutes. The validation of the analytical method should be consistent with the ICH Q2 guidelines.

PMC #3 Description: Provide re-validation data for accuracy and precision using 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.

PMC (1-3) Schedule
Milestones:

Final Report Submission:

04/15/2018

PMC #4 Description: Submit to FDA the appropriate analytical and clinical validation data for the *in vitro* diagnostic assay that identifies homologous recombination deficiency (HRD) subset of epithelial ovarian, fallopian tube, or primary peritoneal cancer patients with a different therapeutic product effect for Niraparib.

PMC (#4) Schedule
Milestones:

Final Report Submission:

12/2017

PMR Description: 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.

PMR Schedule Milestones:	Final Protocol Submission:	<u>06/15/17</u>
	Trial Completion:	<u>11/15/18</u>
	Final Study Report Submission:	<u>02/15/19</u>

Please review the content and dates of the PMC's and PMR. If you have any concerns regarding the content or due dates please respond by **12:00 pm EST, Thursday, March 2, 2017.**

Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
02/28/2017



NDA 208447

MID-CYCLE COMMUNICATION

TESARO, Inc.
Attention: Charles A. Miller
Vice President, Regulatory Affairs
1000 Winter St., Suite 3300
Waltham, MA 02541

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zejula™ (niraparib) Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on February 10, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 10, 2017; 10:00-11:00 am

Application Number: NDA 208447
Product Name: Zejula™ (niraparib)
Requested Indication: Maintenance ^(b)₍₄₎ treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a complete or partial response to platinum-based chemotherapy.

Applicant Name: TESARO, Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Jeannette Dinin, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES

Shefali Agarwal, MD, MPH, Senior Medical Director, Clinical Science
Wei Guo, Director, Biostatistics
Mary Lynne Hedley, PhD, President, Chief Operating Officer
Martin Huber, MD, SVP, Chief Medical Officer
Jennifer Jackson, PhD, SVP, Global Regulatory Affairs and Quality Assurance
Vikram Kansra, PhD, VP, Clinical Pharmacology and Drug Disposition
Dave Lust, MS, Exec. Director, Regulatory CMC
Keith Mikule, PhD, Director Research Pharmacology
Chuck Miller, VP, Regulatory Affairs
Stephen Ruddy, PhD, VP, Pharmaceutical Development
Paul Vancutsem, DVM, PhD, Sr. Director, Preclinical Research and Toxicology
Ilker Yalcin, PhD, VP, Biostatistics

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

A. PMC REQUEST – CMC:

The 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. We will be requesting that you commit to conduct further investigation of your manufacturing process, and that you improve/revise and validate the manufacturing process. The improvement/revision should include for example, incoming material quality controls, unit operations, and/or in-process controls, whichever are necessary.

Final PMC language will be provided at a later date.

B. PMR REQUEST – CLINICAL PHARMACOLOGY:

We will be requesting that you conduct a dedicated pharmacokinetics trial in patients with moderate hepatic impairment to determine an appropriate starting dose of niraparib in patients with moderate hepatic impairment.

C. INDICATION:

We are removing the word [REDACTED] (b) (4) from your January 27, 2017, requested change to the indication. However, we are in agreement with the addition of “a complete or partial”. For inclusion of the word [REDACTED] (b) (4) will need to be submitted.

D. COMPLIMENTARY DIAGNOSTIC:

PMA review

(b) (4)

3.0 INFORMATION REQUESTS

Cardiovascular events and psychiatric events IR sent February 9, 2017.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

In vitro studies showed that niraparib bound to the dopamine, norepinephrine and serotonin transporters and inhibited uptake of norepinephrine and dopamine in cells at concentrations lower than the C_{min} at steady-state in patients receiving the recommended dose. We are particularly concerned about the cardiovascular effects (hypertension, hypertensive crisis and tachyarrhythmia). An IR was sent on February 9, 2017.

No plans at this time for a REMS.

5.0 ADVISORY COMMITTEE MEETING

No plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting is currently scheduled for:

Date: March 7, 2017

Time: 1:00 – 2:00 pm

Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

We intend to send the briefing package to you by March 3, 2017, in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

LALEH AMIRI KORDESTANI
02/28/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/label - Time sensitive
Date: Monday, February 27, 2017 9:52:00 AM
Attachments: image001.png
NDA 208447_DRAFT package insert_02-27-17.docx
Importance: High

Dear Mr. Miller,

Please find attached DRAFT labeling for NDA 208447. Please review the changes and respond with acceptance of the changes or additional changes by email by **9:00 am, Thursday March 2, 2017.**

-

Note, as not all reviews are complete this is not the final agreed upon language.

Please formally submit your response to the NDA after replying by email.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JEANNETTE L DININ
02/27/2017



NDA 208447

INFORMATION REQUEST

Tesaro, Inc.
Attention: Charles A. Miller
Vice President Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, submitted under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act for niraparib capsule, 100mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Process:

1. Provide the reprocessing statement for your drug product manufacturing in accordance with 21 CFR 314.70 and 21 CFR 211.115.
2. We acknowledge your response (dated Feb 10th, 2017) to IR#1 for Drug Product Process, however please confirm your maximum hold time for your future commercial batches (b)(4)

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond to drug process comments by COB February 22, 2017.

Sincerely,

Kristine F. Leahy

-S

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2017.02.21 14:48:25 -05'00'

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA communication: NDA 208447/zejula/IR-clinical/Time sensitive
Date: Thursday, February 09, 2017 10:23:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to inform you that the review team has reviewed the safety signal for hypertension, identified in your NDA submission. We have the following concerns and request for further information:

We have noted that niraparib binds to norepinephrine, serotonin, and dopamine transporters and inhibits uptake of norepinephrine and dopamine *in vitro*, at clinically relevant concentrations. Provide an analysis of all cardiovascular events (stroke, MI, hypertension, hypertensive emergencies, arrhythmias, increases in pulse rate) that occurred in patients treated with niraparib in the safety database (emphasis should be on the NOVA study, with secondary focus on the OCT pool). In this analysis, you should provide information on concomitant medication use that may affect the risk of hypertension and other vascular/ cardiac events including beta-blockers, MAOI's, and concomitant antidepressants/ antipsychotics (including, but not limited to SSRIs, SNRIs, and TCAs).

In addition, the animal studies indicate that niraparib can cross the blood-brain barrier, so you should also provide an analysis of psychiatric events, including anxiety, psychosis, and depression in patients on the NOVA study and the OCT pool. In this analysis, you should provide information on the use of the same concomitant medications above (beta-blockers, MAOI's, SSRIs, SNRIs, and TCAs) in patients who experienced any of these psychiatric events.

Please respond by **noon by February 16, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
02/09/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA communication: NDA 208447/Zejula/mid-cycle communication
Date: Thursday, February 09, 2017 10:34:00 AM
Attachments: image001.png
NDA 208447_MidCycle Agenda.doc
Importance: High

Dear Mr. Miller,

Please find attached the agenda for the mid-cycle communication. The call in information for tomorrow's T-con is as follows:

1. Call one of the following numbers:

Local: 1-301-796-7777

toll free: 1-855-828-1770

2. Follow the instructions that you hear on the phone.

Cisco Unified MeetingPlace meeting ID: (b) (4)

If you have international callers you will need to provide an alternate number.

If you have any additional questions please do not hesitate to ask.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



PDUFA V Program Mid-Cycle Communication Agenda

1. **Applicant/FDA Review Team/ERG Independent Assessor Introductions**
2. **Introductory Comments**
3. **Significant Review Issues:** PMC/PMR update
4. **Information Requests (IRs):** notice of any outstanding IRs
5. **Major Safety Concerns:** cardiovascular events (hypertension and psychiatric events (anxiety, insomnia)
6. **Risk Management:** None
7. **AC Meeting:** None
8. **Late Cycle Meeting Date and Format/Other Projected Milestones:**

Late Cycle Meeting:

Date: March 7, 2017

Time: 1:00 – 2:00 pm

Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

This meeting has been scheduled in accordance to the PDUFA V program. You may choose to cancel this meeting or change it to a T-con if you feel the meeting is unnecessary or if you feel that a face-to-face meeting is unnecessary given the expedited timeline of your application. This application has been identified for early action under an expedited review. We intend to send you the LCM background package by 9:00 am March 3, 2017. If choosing to retain a face to face meeting please send a list of your attendees 1 week prior to the meeting. If you have any foreign visitors please fill out the foreign visitor form and return it no later than **Friday, February 24, 2017**.

Attendees:

Geoffrey Kim, MD, Director, Division of Oncology Products 1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
Jeannette Dinin, Regulatory Project Manager, DOP1
ERG Independent Assessor

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/s/

JEANNETTE L DININ
02/09/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/Late Cycle meeting
Date: Friday, February 03, 2017 10:46:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to inform you that your Late Cycle meeting has been scheduled for NDA 208447.

The meeting is scheduled as follows:

Date: March 7, 2017
Time: 1:00 – 2:00 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

This meeting has been scheduled in accordance to the PDUFA V program. You may choose to cancel this meeting or change it to a T-con if you feel the meeting is unnecessary or if you feel that a face to face meeting is unnecessary given the expedited timeline of your application. An agenda will be sent by 9:00 am March 3, 2017. If choosing to retain a face to face meeting please send a list of your attendees 1 week prior to the meeting. If you have any foreign visitors please fill out the foreign visitor form and return it no later than **Friday, February 24, 2017**.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Tel: 240-402-4978

Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
02/03/2017

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/Zejula/container label - time sensitive
Date: Thursday, February 02, 2017 2:40:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following changes to your container label:

1. Relocate 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 U.S. healthcare professionals are accustomed to.
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 201.100 (b) (4) for (b) (4) products and to reduce information crowding on the principal display panel.
4. Delete or move 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 (b) (4)
(b) (4) 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 (b) (4) codes. Please clarify what the two (b) (4) codes are for, and what information is contained in the two (b) (4) codes.

Please respond by no later than **COB Monday February 13, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products

Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
02/02/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/NDA split
Date: Wednesday, February 01, 2017 8:48:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to inform you that NDA 208447 will not be administratively split into NDA 1 and NDA 2. The user fee for the non-orphan designation indications will be tracked within the original NDA. Thank you for working with us to resolve the user fee issue, your user fee for NDA 208447 has been received.

Sincerely,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
02/01/2017



NDA 208447

INFORMATION REQUEST

Tesaro, Inc.
Attention: Charles A. Miller
Vice President Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act for niraparib capsule, 100mg.

We also refer to your October 31, 2016, submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Biopharmaceutics:

1. We acknowledge your justification for [REDACTED] (b) (4) the dissolution test. Since Tier-2 testing is included in the proposed dissolution method [REDACTED] (b) (4) We therefore recommend [REDACTED] (b) (4) the dissolution method and revise the Specifications table accordingly.

Please respond to Biopharmaceutics comments by COB February 6, 2017.

Drug Product Process:

[REDACTED] (b) (4)

Drug Product:

1. Regarding the packaging system used to store and transport bulk capsules from the manufacturing site to the primary packaging site:

- (a) Describe each component in the packaging system including the dimensions, (b) (4) and materials of composition.
- (b) Identify the supplier for each component and provide a copy of the supplier's certificate of analysis (CoA) for each component used to package the NDA registration capsule batches.
- (c) Provide the acceptance specification for each component. Also, identify the tests performed for each component lot for acceptance and what data is accepted from the supplier's CoA. Acceptance of each lot of each packaging component should include at least testing for identity. We remind you that holding bulk (b) (4) will necessitate a revision of the control strategy and the submission of supporting stability studies.

2. Regarding the information in module 3.2.P.4:

- (a) Identify the supplier of (b) (4) and magnesium stearate and provide a copy of the supplier's CoA for the lots used in the NDA registration batches of capsules.
- (b) Provide the acceptance specification for (b) (4) magnesium stearate and indicate which test results are typically taken from the supplier CoA for acceptance of a lot. For acceptance, testing on each excipient lot should include at least identity and purity for magnesium stearate; (b) (4)
- (c) Regarding the acceptance specification for hard gelatin capsules, indicate which tests results are typically taken from the (b) (4) CoA for acceptance of a lot.

3. Regarding the proposed drug product release specification (module 3.2.P.5.1):

- (a) Add an identity test for the tosylate anion. This material can be detected by Metrics method AM-1971.
- (b) Revise the test for Degradation Products to report all compounds detected at or above the limit of quantitation established in the method validation studies for Metrics method AM-1971.
- (c) Describe the scheme for collecting samples for the content uniformity test.

4. Regarding the method descriptions (module 3.2.P.5.2):

- (a) Provide a detailed description of each analytical method intended for use after NDA approval. The description should include any method variations established as acceptable in the validation studies. In the application, method descriptions are provided as a series of summaries; in a Metrics document; and in the Metrics method validation report. However, some of the method validation reports propose changes which are not included in the Metrics documents.
- (b) For Metrics method AM-1971:
 - i) Revise the change history to include the date of implementation for each change.

- ii) Revise the system suitability criteria for assay and content uniformity to include a criterion for baseline stability and column efficiency.
 - iii) Revise the calculations to correct for (b) (4) in the sample. The reference standard has this correction and the limit (b) (4) in the sample is significant.
 - iv) Either revise the preparation of the stock solutions for assay and content uniformity to indicate that the solutions must be used immediately or provide data to establish acceptable storage conditions and maximum storage times.
- (c) For (b) (4) method AN-1974:
- i) Revise the change history to include the date of implementation for each change.
 - ii) Revise the system suitability criteria to include baseline stability and column efficiency

5. Regarding (b) (4) method validation reports 10137 and 11217:

- (a) The (b) (4) reports include references to a “draft method”; specify which version of the method was validated.
- (b) The submitted validation study is based on sampling at (b) (4) minutes as indicated in the release specification. Therefore, the study is not acceptable. Provide an acceptable validation study for this method using the appropriate dissolution parameters.

6. Regarding (b) (4) method validation report 9819:

- (a) The data provided in the method summaries and the (b) (4) validation reports are not the same, please explain this discrepancy.
- (b) The (b) (4) report includes references to a “draft method”; specify which version of the method was validated.
- (c) Provide an explanation for the out of specification results for accuracy of the 100% level sample. Having 5 of 18 test results outside the criterion range is not acceptable despite meeting the criterion for percent relative standard deviation.

7. Regarding the information in module 3.2.P.5.4:

- (a) Provide sample HPLC chromatograms for assay method-1 for blank, placebo, reference standard, and test sample used in the analyses for impurities and for assay.
 - (b) In table 10, specify the dates for testing by the HPLC method in the release and commercial specification; describe the storage conditions; provide the values for individual capsules and the relative standard deviation.
 - (c) Provide the results of (b) (4) testing on the NDA registration batches of capsules. (b) (4)
- (b) (4)

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond to these comments by COB February 10, 2017.

Sincerely,

Kristine F. Leahy -S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001815977, cn=Kristine F. Leahy -S
Date: 2017.01.31 16:12:54 -0500'

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/IR - consent form/ Time Sensitive
Date: Friday, January 27, 2017 9:18:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request all informed consent form versions identified in CSR Appendix 16.1.3. associated with Denmark. Alternatively, you may identify the location of this information in your current application.

Please respond if possible by **COB today, January 27, 2017**. If you are unable please respond by the requested time please respond by **no later than 9:00 am Monday, January 30, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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JEANNETTE L DININ
01/27/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/PSP and waiver request
Date: Thursday, January 26, 2017 2:56:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request a Pediatric Study Plan and full waiver request be submitted to NDA 208447 for your non-orphan designation indications, fallopian tube and primary peritoneal. Please formally submit to the NDA by noon on **Monday, January 30, 2017**. Please be sure to include both a word a pdf version of the waiver.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
01/26/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/Clin pharm IR - Time Sensitive
Date: Wednesday, January 25, 2017 10:01:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following information in reference to NDA 208447:

1. Please provide your assessment of the extent of liver involvement in the disposition of niraparib. Specifically, assess which carboxylesterase isozyme (hCES1 [predominantly hepatic] or hCES2 [hepatic and intestinal]) is involved in the hydrolysis of niraparib to form M1.¹⁻³ This information will be utilized to further assess the need for dose adjustment in patients with hepatic impairment due to exposure alterations.

References:

1. Ross MK., Crow JA., Human carboxylesterases and their role in xenobiotic and endobiotic metabolism. J Biochem Mol Toxicol. 2007; 21(4):187-96
2. Taketani M., Shii M., Carboxylesterase in the liver and small intestine of experimental animals and human. Life Sci. 2007; 81(11):924-32.
3. Imai T., Taketani M., Substrate specificity of carboxylesterase isozymes and their contribution to hydrolase activity in human liver and small intestine. Drug Metab Dispos. 2006; 34(10):1734-41

Please respond by **COB January 30, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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JEANNETTE L DININ
01/25/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA communication: NDA 208447/Zejula/IR clinical - Time Sensitive
Date: Wednesday, January 25, 2017 10:31:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following dataset guidance in reference to NDA 208447. We are working on analyzing the safety data in the OCT treatment pool, using the analysis dataset ADAE submitted in the ISS on 10/27/16 (submission seq 0003), but are having difficulty isolating the correct patients (the denominator, in particular), compared with your study reports. For instance, the OCT pool includes n=384 patients, and it appears that n=369 experienced at least 1 TEAE, however we have been unable to isolate these patients from the specified dataset. Please provide us with guidance on which dataset is the correct one to use, and which flags in the dataset will allow us to perform the appropriate analyses.

Please respond by no later than **3:00 pm EST today, January 25, 2017**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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JEANNETTE L DININ
01/25/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/IR - Clinical/ Time Sensitive
Date: Wednesday, January 25, 2017 2:00:00 PM
Attachments: Subsequent therapies after NOVA study participation.docx
image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request that you Provide us with a table, as well as an analysis dataset to derive the data in the table, so that we may do an analysis of the specific agents that patients went on to receive after discontinuing from the NOVA study (attached is an example of what we are interested in seeing in such a table). This will help in our analysis of your secondary endpoints, including time to first subsequent therapy, chemotherapy-free interval, and time to second subsequent therapy.

Please provide both the table and the dataset by **12:00 pm EST, Friday, January 27, 2017**. Please provide by 1) email to facilitate review 2) formal submission to the NDA

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



	gBRCAm cohort n=203		Non-gBRCA cohort			
			HRD+ N=162		Overall N=350	
Subsequent chemotherapy agents	Niraparib N=138	Placebo N=65	Niraparib N=106	Placebo N=56	Niraparib N=234	Placebo N=116
Number of patients receiving any subsequent anticancer therapy						
Specific subsequent anticancer agents						
Carboplatin						
Gemcitabine						
Paclitaxel						
Liposomal doxorubicin						
Other PARP inhibitor (specify)						
Niraparib						
Bevacizumab						
other specific agents of interest.... etc						

APPEARS THIS WAY ON ORIGINAL

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/s/

JEANNETTE L DININ
01/25/2017



NDA208447

GENERAL ADVICE

TESARO, Inc.
Attention: Charles A. Miller
Vice President, Regulatory Affairs
1000 Winter St.
Suite 3300
Waltham, MA 02541

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zejula™ (niraparib).

The purpose of this letter is to inform you that all indications listed in NDA 208447 have not been granted Orphan designation. The Office of Orphan Product Development (OOPD) has confirmed that your orphan designation is for ovarian cancer only and does not cover primary peritoneal or fallopian tube cancer. As such a user fee is required for the primary peritoneal and fallopian tube cancer indications. You have 5 days to pay the user fee or a "No User Fee Received" letter will be filed. Once the user fee is received your NDA will be administratively split into original NDA 1 and NDA 2.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: Orphan Designation letter



Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

APR 30 2010

Merck Sharp & Dohme Corp.
351 N. Sumneytown Pike
Upper Gwynedd, Pennsylvania 19454

Attention: Lou Ann Eader, Ph.D.
Director, Worldwide Regulatory Affairs

Re: Designation Request # 10-3065

Dear Mr. Simes:

Reference is made to your request for orphan-drug designation dated March 30, 2010, of (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine (tosylate monohydrate salt)(company name: MK-4827) for "treatment of ovarian cancer." Please also refer to our letter dated April 1, 2010.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine (tosylate monohydrate salt)(company name: MK-4827) is granted for *treatment of ovarian cancer*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Peter L. Vaccari, R.Ph., at (301) 796-8675. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy R. Coté". The signature is fluid and cursive, with a large initial "T" and "C".

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

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/s/

CHRISTY L COTTRELL
01/24/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/MidCycle communication
Date: Wednesday, January 18, 2017 11:15:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to let you know the time and date for scheduled Mid-Cycle communication. Mid-Cycle communication is currently scheduled as a 1 hour T-con for Friday, February 10, 2017, from 11:00 am – 12:00 pm. Call in information and an agenda will be provided to you a few days prior to the scheduled T-con. Please note, depending on the agenda, the T-con time may be reduced. If you have any international callers please provide the call in information.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
01/18/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/zejula/IR - clinical(PRO)/ Time Sensitive
Date: Tuesday, January 10, 2017 8:04:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following information in regards to NDA 208447:

We are in the process of working to better understand the patient reported outcomes data provided to us by sponsors and would like to request a data table based on the completeness of the PRO instruments based on each of the following assumptions:

- Number of patients who were assessable per cycle (on study who were scheduled to receive an assessment).
- Number of patients with completed assessments for PRO instruments as per instrument instructions (e.g. for the FOSI, data are able to be evaluated as long as greater than 50% of questions are answered, in this case 5 or more of the 8 questions). It was not clear whether the analysis was done based on this assumption or as stated on page 15 of the PRO report if at least one item was answered.
- Please clarify what is meant by the HUI in terms of the EQ5D data. The HUI is another assessment from McMasters University that is often used in determining QALY. Was this alternate instrument used as well or was this the health state index that is able to be derived from the EQ5D assessment?
- Please clarify the origin of the neuropathy questions—are these from a validated instrument or were these generated for use in this particular protocol

Please provide by **COB, Wednesday, January 11, 2017**. Please provide by 1) email to facilitate review 2) formal submission to the NDA.

If more time is needed to gather the requested information please let me know as soon as possible.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
01/10/2017

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/zejula/IR - clin pharm/ Time Sensitive
Date: Tuesday, January 03, 2017 8:57:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following information for NDA 208447:

1. Please provide datasets and define files for the raw PK concentrations and derived PK parameters for studies of PN001, PR-30-5015-C, PR-30-5011-C2-FE. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Please address the following additional labeling issues in your updated label:
 - a. According to regulation 21 CFR 201.57(c)(13)(i)(B), exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known in section 12.2 of the proposed labeling for Zejula®. If this information is unknown, this subsection must contain a statement about the lack of information.”
 - b. Provide your proposed language to describe the drug’s effects on QTc prolongation under the subheading “Cardiac Electrophysiology” in section 12.2.

Please provide by **COB January 6, 2017**. Please provide by 1) email to facilitate review 2) formal submission to the NDA

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
01/03/2017

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, December 20, 2016 12:07 PM
To: 'cmiller@tesarobio.com'
Cc: Dinin, Jeannette; Robertson, Kim
Subject: FDA Communication: NDA 208447/zejula/clinical IR - time sensitive

Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following information in reference to NDA 208447: please reply to all when responding due to holiday leave.

Clinical IR:

We are having difficulty confirming the numbers you have in your Table 21 in the CSR (prior treatment lines for of therapy ovarian cancer). For example, using ADCM dataset and cross-referencing this patient's CRF:

Patient 001007-00017: On CRF, she received:

- 1) Regimen 1- taxol, cisplatin, bevacizumab (labeled as "adjuvant")**
- 2) Regimen 2- bevacizumab (labeled as "adjuvant")**
- 3) Regimen 3- Doxil, carboplatin. (labeled as "metastatic").**

Confirm how many regimens you counted this patient has having (both in categories "number lines of chemotherapy" and "number of lines of platinum therapy") in CSR table 21. Direct us as to which parameters to use in the ADCM dataset (or other dataset) to understand how lines of prior therapy were derived (for this and all patients), as listed in Table 21, so that we may perform this analysis. You should clarify whether you considered a maintenance regimen (such as bevacizumab) to be separate line of therapy, or if it depended upon certain factors (i.e. switch maintenance).

Please respond by no later than 2:00 pm EST., on Thursday, December 22, 2016. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

Office of Hematology & Oncology Products (OHOP) / CDER/ FDA

10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993

sakar.wahby@fda.hhs.gov

(P): 240-402-5364

(F): 301-796-9845

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/s/

SAKAR M WAHBY
12/20/2016

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/zejula/clin pharm IR - time sensitive
Date: Monday, December 19, 2016 3:38:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following information in reference to NDA 208447:

1. Using a power model¹, conduct a statistical evaluation of dose proportionality for C_{\max} and AUC after single and multiple doses, including all dose levels investigated in trial PN001.
2. Evaluate the time-dependence of niraparib pharmacokinetics by conducting the following assessments:
 - a. Linear scale plot of the observed steady state trough concentrations ($C_{\text{trough,ss}}$) versus time or treatment cycles
 - b. Linear scale plot of the observed apparent steady state clearance (CL/F) versus time or treatment cycle
 - c. Statistical and graphical assessments of the similarity between the available $AUC_{0-\text{inf}}$ after single dose and AUC_{tau} at steady state

Reference:

1. *Smith, B. P., Vandenhende, F.R., Confidence Interval Criteria for Assessment of Dose Proportionality, Pharm. Res., 17(10):1278-1283 (2000)*

Please respond, with a written response along with relevant plots, datasets and programs, by no later than COB January 4, 2017. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
12/19/2016



NDA 208447

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

TESARO, Inc.
1000 Winter Street
Suite 3300
Waltham, MA 02451

ATTENTION: Charles A. Miller
Vice President Regulatory Affairs

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Niraparib Capsules, 100mg.

We also refer to your correspondence, dated and received November 2, 2016, requesting review of your proposed proprietary name, Zejula.

We have completed our review of the proposed proprietary name, Zejula and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 2, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Jeanette Dinin, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4978.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/16/2016



NDA 208447

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

TESARO, Inc.
Attention: Charles A. Miller
Vice President, Regulatory Affairs
1000 Winter St.
Suite 3300
Waltham, MA 02541

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated October 31, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zejula™(niraparib).

We also refer to your amendment dated November 23, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 30, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 19, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling

and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is February 6, 2017.

We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following information by close of business, December 28, 2016:

1. Confirm that all the batches of the product used in the pivotal clinical studies, and the to-be-marketed product will be manufactured at the same site. Provide the appropriate formulation bridging data if the clinical batches were manufactured at multiple sites.
2. Revise Table 5 of the Pharmaceutical Development report (Module 3.2.P.2) to include clinical study related details, such as phase of the clinical study, associated with each of the batches/lots.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

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)”.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 6, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see: <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GEOFFREY S KIM
12/16/2016

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/clin pharm IR - Time Sensitive
Date: Thursday, December 15, 2016 7:49:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller

The purpose of this email is to request the following information for NDA 208447:

In reference to your report, "Population pharmacokinetic and pharmacodynamic modeling of niraparib" in module 5.3.3.5 of NDA208447 submitted on October 31, 2016:

- Provide NONMEM code and datasets for PopPK analysis which can be verified by FDA reviewer. In addition, provide clarification on criteria used for hepatic function category in your PopPK analysis. Please reanalyze the effect of hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria. Update your PopPK report and submit the code/datasets by **COB January 2, 2017**.
- Please provide details on how the exposure metrics were calculated in the Exposure-Response (ER) analysis. As majority of patients underwent dose modification, the average daily exposure up to the time of event of interest based on actual dosing record should be used in ER analysis for efficacy and safety. Conduct the following analysis and update your ER report and submit the code/datasets which can be verified by FDA reviewer. **Please provide by 9:00 am January 16, 2017**.
 - Logistic regression analysis for ER for safety should be conducted. Safety events should include the FIRST occurrence of the following safety events: any grade anemia, grade $\frac{3}{4}$ anemia, any grade thrombocytopenia, grade $\frac{3}{4}$ thrombocytopenia, any grade neutropenia and grade $\frac{3}{4}$ neutropenia. In addition, include the time of event for each individual in the datasets.
 - Time-to-event analysis should be conducted for ER for PFS. Provide K-M analysis with exposure quartile and multivariate cox proportional hazard analysis to adjust for the other prognostic factors (e.g., ECOG, baseline tumor size).

Reference is made to your slides at Applicant Orientation Meeting (AOM) on November 28, 2016

- Based on the slide #31, the dose reduction appeared to have marginal effect on the risk of anemia. Please further evaluate whether the required dose reduction is an optimal approach to manage the anemia given the potential loss of efficacy at lower dose and the existing other measures (e.g., dose interruption and transfusion). The following analysis may be considered as starting point based on the data in Study PR-30-5011-C:
 - A time-course change of CBC/hemoglobin in patients
 - Comparison of CBC/hemoglobin/incidence of anemia at three different dose levels (300 mg QD, 200 mg QD, 100 mg QD)
 - For patients underwent dose reductions, provide comparison of

- CBC/hemoglobin before and after dose reduction happened.
- Please provide this information by **9:00 am, January 16, 2017**. As part of your submission for record keeping purposes please submit a copy of the slides presented during your AOM.

Please respond by no later than the listed date for each question. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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JEANNETTE L DININ
12/15/2016

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/Zejula/Clinical-stats IR/ Time sensitive
Date: Thursday, December 15, 2016 7:57:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller

The purpose of this email is to respond to your December 12, 2016, submitted IR response regarding study NOVA of NDA 208447. We have the following further information requests:

1. Per your response to the statistical IR #3 (dated November 30, 2016), we understand that your primary PFS analysis was based on the IRC global review which could have updated (changed) any previous timepoint responses for some patients. Please conduct a PFS analysis without considering the IRC global review, but based on programmatically derived disease progression data from the IRC timepoint-by-timepoint raw lesion measurements only. Please submit SAS dataset and SAS program for the above PFS data in the format as requested in the statistical IR #3.
2. Per your response to the statistical IR #4a (dated November 30, 2016), you have evaluated the PRO data at 8 weeks following progressive disease. Please specify the variable(s) used to identify the post-progression assessment in dataset ADQS. In dataset ADQS, there is no visit labelled as post-progression assessment.

Please respond by **COB December 22, 2016**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
12/15/2016



**METHOD VERIFICATION
MATERIALS RECEIVED**

NDA 208447

December 12, 2016

Charles Miller
cmiller@tesarobio.com
Tesarro Inc.
1000 Winter Street, Suite 3300
Waltham MA 02451

Dear Charles Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zejula (Niraparib), 100 g capsules and to our November 18, 2016, letter requesting sample materials for method verification testing.

We acknowledge receipt on December 9, 2016, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

**Laura C.
Pogue -S**

Digitally signed by Laura C. Pogue -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Laura C. Pogue -
S,
0.9.2342.19200300.100.1.1=2000606027
Date: 2016.12.12 10:41:59 -06'00'

Laura C. Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: FDA Communication: NDA 208447/niraparib/IR - protocol amendments/ Time sensitive
Date: Monday, December 12, 2016 10:32:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request that you complete the chart below regarding protocol amendments:

PR-30-5011-C (NOVA) Version	Date released	# patients enrolled
Original protocol	3/21/13	
Amendment 1	5/3/13	
Amendments 2 and 3	4/9/14	
Amendment 4	12/4/14	
Amendment 5	9/11/15	
Amendment 6	3/9/16	
US-only amendments		
US-1	3/10/15	
US-2	9/11/15	
US-3	3/9/16	

Please respond by no later than **9:00 am, Tuesday, December 13, 2016**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Thank you,

Jeannette Dinin
Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
12/12/2016

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/Zejula/name IR - Time Sensitive
Date: Monday, December 12, 2016 11:15:00 AM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to confirm whether the requested proprietary name should read (b) (4) "Zejula™", your current submitted information alternates between both formats. Please confirm which is correct.

Please confirm by **COB today, December 12, 2016**. Please respond by both email and formal submission.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
12/12/2016

From: Dinin, Jeannette
To: ["Chuck Miller"](#)
Subject: RE: FDA Communication: NDA 208447/niraparib/IR - stats/ Time Sensitive
Date: Monday, December 05, 2016 2:13:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to provide the clarification requested below:

- On page 90 (section 5.2) of the PRO report, it says “a mixed-effects growth-curve model adjusting for fixed and random covariates (patient, time, **baseline demographic values, and the 3 stratification factors**) was conducted to assess “. We ask for an analysis without the adjustment of baseline demographic values and stratification factors. The baseline score of PRO should be kept.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



From: Chuck Miller [<mailto:cmiller@tesarobio.com>]
Sent: Monday, December 05, 2016 10:50 AM
To: Dinin, Jeannette
Subject: RE: FDA Communication: NDA 208447/niraparib/IR - stats/ Time Sensitive

Good morning Jeanette,

We have one point that requires some clarification. In addition, we may be coming back with an additional question in the next day or so. I have bolded the query number and the question we have just to make it easier to find.

In **part 4c** of the queries below, FDA requested an analysis without adjustment by “baseline demographic values” and “stratification factors”. The original longitudinal model in the report included stratification factors, baseline value, treatment, visit, treatment-by-visit interaction and individual patient effect. We would like to clarify what is meant by the baseline demographic values since the model did not include any demographic variables. We believe that the baseline score is important to keep in the ANCOVA model as it adjusts for potential baseline imbalances and improves the precision of the estimates. **Does the agency mean removing the baseline score for the Health Outcome instrument score?** If so, please note the aforementioned caveats regarding imbalances and precision.

Best regards,

Chuck

From: Dinin, Jeannette [<mailto:Jeannette.Dinin@fda.hhs.gov>]
Sent: Wednesday, November 30, 2016 2:17 PM
To: Chuck Miller
Subject: FDA Communication: NDA 208447/niraparib/IR - stats/ Time Sensitive
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following statistical information for NDA 208447:

1. Please explain how the final disease progression date was determined for patients PR-30-5011-C-045004-00002 and PR-30-5011-C-045003-00012.
2. In the dataset “RS”, for each patient only one assessment data from central oncologist is available. Does that mean the central oncologist only evaluated each patient once? Please clarify.
3. Please perform the following analyses using data prior to or on the clinical cutoff date, May, 30 2016.
 - a. Please derive disease progression data based on IRC raw lesion measurement and clinical review following the progression criteria specified in the study SAP section 5.1.1 using a SAS program. This is to check whether the central reviewers followed the protocol specified progression criteria or not.
 - b. Please derive disease progression data based on investigator raw lesion measurement and clinical data following the progression criteria specified in the study SAP section 5.1.1 using a SAS program. This is to check whether the investigator followed the protocol specified progression criteria or not.
 - c. Please perform PFS analyses based on the data derived above for IRC and investigator.

Please submit the SAS program and SAS dataset (.xpt) for the above PFS analyses. The SAS dataset should include the following information:

	Data needed in the SAS dataset
Patient info	Subject ID,

	Randomized arm, Randomization date
Central Radiology Data	Status of progression following RECIST1.1 per central radiologist assessment (yes vs. no), Date of progression following RECIST 1.1 per central radiologist assessment, Reason of progression following RECIST1.1 per central radiologist assessment (target lesion PD vs. non-target lesion PD vs. new lesion)
Central Clinical Data	Status of progression per central oncologist (yes vs. no), Date of progression per central oncologist, Reason of progression per central oncologist (PDC2 vs. PDC3)
Investigator data	Status of progression per investigator assessment (yes vs. no), Date of progression per investigator assessment, Reason of progression per investigator assessment (RECIST PD: target lesion PD vs. non-target lesion PD vs. new lesion; clinical PD: PDC2 vs. PDC3)
Last assessment	Last assessment date for censoring per central review, Last assessment date for censoring per investigator
PFS analysis data	PFS time in month per IRC, PFS censoring status per IRC, PFS time in month per INV, PFS censoring status per INV

- d. Please use data derived above to perform a PFS analysis using IRC radiology progression data and central clinical progression data (i.e., use clinical PD date from the central oncologist if investigator and central oncologist agreed on the occurrence of clinical PD).
4. The following requests are for patient-reported outcomes:
- As specified in the study SAP, PROs were collected every 8 weeks for the first year, then every 12 weeks while on study treatment. Once a patient discontinued treatment, PRO evaluations were performed at that time and 1 additional time 8 weeks following discontinuation. However, in the PRO report, no data from treatment discontinuation assessment and 8-week post treatment discontinuation were provided. Instead, data from “post-progression assessment” were provided. Please explain.
 - In dataset ADQS, we noted that some observations with variable visit= “999” and visitnum = “patient reported outcomes”. What does that visit refer to?
 - For the longitudinal analysis of each instrument, please perform an analysis without adjustment by baseline demographic values and stratification factors.

Please respond by **COB, December 9, 2016**. Please respond by 1) email to facilitate review
2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-4978

Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
12/05/2016



NDA 208477

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

TESARO, Inc.
1000 Winter Street
Suite 3300
Waltham, MA 02451

ATTENTION: Charles A. Miller
Vice President Regulatory Affairs

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Niraparib Capsules, 100mg.

We acknowledge receipt of your correspondence, dated and received November 2, 2016, requesting a review of your proposed proprietary name, Zejula.

If the application is filed, the user fee goal date will be January 31, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, please contact me at (301) 796-0942. For any other information regarding this application, contact Jeannette Dinin, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4978.

Sincerely,

{See appended electronic signature page}

Frances Fahnbulleh, PharmD, RPh.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

FRANCES G FAHNBULLEH
12/01/2016

From: Dinin, Jeannette
To: [Chuck Miller](#)
Subject: FDA Communication: NDA 208447/niraparib/IR - stats/ Time Sensitive
Date: Wednesday, November 30, 2016 2:17:00 PM
Attachments: image001.png
Importance: High

Dear Mr. Miller,

The purpose of this email is to request the following statistical information for NDA 208447:

1. Please explain how the final disease progression date was determined for patients PR-30-5011-C-045004-00002 and PR-30-5011-C-045003-00012.
2. In the dataset “RS”, for each patient only one assessment data from central oncologist is available. Does that mean the central oncologist only evaluated each patient once? Please clarify.
3. Please perform the following analyses using data prior to or on the clinical cutoff date, May, 30 2016.
 - a. Please derive disease progression data based on IRC raw lesion measurement and clinical review following the progression criteria specified in the study SAP section 5.1.1 using a SAS program. This is to check whether the central reviewers followed the protocol specified progression criteria or not.
 - b. Please derive disease progression data based on investigator raw lesion measurement and clinical data following the progression criteria specified in the study SAP section 5.1.1 using a SAS program. This is to check whether the investigator followed the protocol specified progression criteria or not.
 - c. Please perform PFS analyses based on the data derived above for IRC and investigator.

Please submit the SAS program and SAS dataset (.xpt) for the above PFS analyses. The SAS dataset should include the following information:

	Data needed in the SAS dataset
Patient info	Subject ID, Randomized arm, Randomization date
Central Radiology Data	Status of progression following RECIST1.1 per central radiologist assessment (yes vs. no), Date of progression following RECIST 1.1 per central radiologist assessment, Reason of progression following RECIST1.1 per central radiologist assessment (target lesion PD vs. non-target lesion PD vs. new lesion)
Central Clinical Data	Status of progression per central oncologist (yes vs. no), Date of progression per central oncologist, Reason of progression per central oncologist (PDC2 vs. PDC3)
Investigator data	Status of progression per investigator assessment (yes vs. no), Date of progression per investigator assessment,

	Reason of progression per investigator assessment (RECIST PD: target lesion PD vs. non-target lesion PD vs. new lesion; clinical PD: PDC2 vs. PDC3)
Last assessment	Last assessment date for censoring per central review, Last assessment date for censoring per investigator
PFS analysis data	PFS time in month per IRC, PFS censoring status per IRC, PFS time in month per INV, PFS censoring status per INV

- d. Please use data derived above to perform a PFS analysis using IRC radiology progression data and central clinical progression data (i.e., use clinical PD date from the central oncologist if investigator and central oncologist agreed on the occurrence of clinical PD).
4. The following requests are for patient-reported outcomes:
- a. As specified in the study SAP, PROs were collected every 8 weeks for the first year, then every 12 weeks while on study treatment. Once a patient discontinued treatment, PRO evaluations were performed at that time and 1 additional time 8 weeks following discontinuation. However, in the PRO report, no data from treatment discontinuation assessment and 8-week post treatment discontinuation were provided. Instead, data from “post-progression assessment” were provided. Please explain.
 - b. In dataset ADQS, we noted that some observations with variable visit= “999” and visitnum = “patient reported outcomes”. What does that visit refer to?
 - c. For the longitudinal analysis of each instrument, please perform an analysis without adjustment by baseline demographic values and stratification factors.

Please respond by **COB, December 9, 2016**. Please respond by 1) email to facilitate review
2) formal submission to the NDA.

Thank you,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-4978
Jeannette.Dinin@fda.hhs.gov



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/s/

JEANNETTE L DININ
11/30/2016

From: [Dinin, Jeannette](#)
To: [Chuck Miller](#)
Cc: ["Jennifer Jackson"](#)
Subject: FDA Communication: NDA 208447/niraparib/AOM and technical walkthrough meetings
Date: Monday, October 17, 2016 3:01:00 PM
Attachments: Application Orientation_general information.pdf
Foreing visitor form.doc
Importance: High

Dear Chuck,

Please find attached information regarding FDA's request for an Application Orientation Meeting (AOM) for upcoming NDA 208447. We would like to invite you to come here and present your application. The meeting will occur on:

Meeting Date and Time: November 28, 2016; 10:30-11:30 am
Meeting Location: White Oak, Building 22, Room 2205

Because space is limited please limit your attendees to approximately 12 participants. Please be sure to fill out the foreign visitor form for any non-U.S. citizens and submit it 2 weeks prior to the AOM. Additional details regarding the AOM can be found in the attachment. Slides for the AOM presentation should be provided by **COB, on Wednesday, November 23, 2016.**

Additionally, immediately prior to the AOM we have scheduled a technical walk through meeting. The meeting is scheduled as follows:

Meeting Date and Time: November 28, 2016; 9:30-10:30 am
Meeting Location: White Oak, Building 22, Room 1311

Please send me your slides for the technical walk through by **COB, Friday November 25, 2016.** Please note, these meetings are based on your CURRENT timeline of submitting the final piece of your application to start the PDUFA cock. Any change in your timeline may require us to reschedule.

If you any questions please do not hesitate to ask.

Sincerely,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products

OND/CDER/FDA

Phone: 240-402-4978

Fax: 301-796-9845

Email: Jeannette.Dinin@fda.hhs.gov

OHOP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OHOP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees
2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.
4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.
5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.
6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.
7. Regulatory history, including the following:
 - Orphan Drug designation, Fast Track designation
 - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
 - Key Outcomes from FDA Interactions
 - EOP2 Meeting

- Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
- Pre-NDA/BLA meeting
- Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

You should also present results of the following, as appropriate:

- Clinical study sites (foreign or domestic)
- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data
10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
 - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.
11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities
12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).
13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU)).
14. Risk/benefit profile for drug/biologic
15. Summary
16. Q & A

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	November 28, 2016; 9:30 am
MEETING ENDING DATE AND TIME	November 28, 2016; 12:00 pm
PURPOSE OF MEETING	eCTD navigation meeting and Application Orientation Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22, Room 2205 & 1313
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Jeannette Dinin Regulatory Project Manager Building 22, Rm. 2108 240-402-4978
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JEANNETTE L DININ

11/18/2016

email sent on October 17, 2016



**REQUEST FOR METHOD
VERIFICATION MATERIALS**

NDA 208447

November 18, 2016

Charles Miller
cmiller@tesarobio.com
Tesaro Inc.
1000 Winter Street, Suite 3300
Waltham MA 02451

Dear Charles Miller:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zejula (Niraparib), 100 g capsules.

We will be performing method verification studies on Zejula (Niraparib), 100 g capsules as described in NDA 208447.

In order to perform the necessary testing, we request the following sample materials and equipment:

Method, current version

- 1) AM-1842 FTIR for Identification (Drug Substance)
- 2) AM-1843 FTIR for Identification (Drug Product)
- 3) AM-1921 ID, Assay, and Impurities (Drug Substance)
- 4) AM-1971 ID, Assay, and Impurities (Drug Product)
- 5) AM-1814 HPLC for Chiral Enantiomer (Drug Substance)
- 6) AM-1974 Dissolution (Drug Product)
- 7) (b) (4) (Drug Product)

Chemicals, Samples and Reference Standards

- 1) Niraparib tosylate monohydrate reference standard (3 g x 2)
- 2) Niraparib tosylate monohydrate drug substance (5 g x 2)
- 3) Impurity A Impurity B and Impurity E (b) (4) mg each
- 4) (b) (4)
- 5) (b) (4)
- 6) (b) (4)
- 7) (b) (4)
- 8) (b) (4)



- 9) [REDACTED] (b) (4)
10) [REDACTED]
11) Niraparib 100 mg Capsules Drug Product (100 capsules x 2)

Equipment

- 1) HPLC Column: Waters SymmetryC18, 150 x4.6 mm, 3.5 µm
- 2) HPLC Column: Chiralpak, AS-H, 250 x 4.6 mm, 5 µm
- 3) GC Column: J&W DB-FF AP, 30 m x 0.32 mm, 1 µm, or equivalent
- 4) HPLC Column: Agilent Zorbax SB-Aq, 4.6 x 50 mm, 5 µm

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,
**Laura C.
Mecker -S**

Digitally signed by Laura C. Mecker -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000606027,
cn=Laura C. Mecker -S
Date: 2016.11.18 11:03:07 -06'00'

Laura C Pogue, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208447

NDA ACKNOWLEDGMENT

TESARO, Inc.
Attention: Charles A. Miller
Vice President, Regulatory Affairs
1000 Winter St.
Suite 3300
Waltham, MA 02541

Dear Mr. Miller:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Zejula[®] (niraparib)

Date of Application: October 31, 2016

Date of Receipt: October 31, 2016

Our Reference Number: NDA 208447

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 30, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JEANNETTE L DININ
11/16/2016

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/Zejula/TMF IR - Time sensitive
Date: Monday, November 14, 2016 11:13:00 AM
Importance: High

Dear Chuck,

1. You should clarify the location of your Trial Master File. It appears that it is located at (b) (4). Confirm whether this is the case (or not), and provide us with the address, contact person, and phone number for (b) (4). The trial master file should include a listing of all relevant contacts involved in the conduct of the NOVA trial (PR-30-5011-C), as well as the roles of each participant.
2. Please confirm the name and contact information for the main principal investigator in the US for the NOVA trial.
3. We will need the charter that was used by the blinded central radiology review committee. Either provide the location of this charter in your NDA submission, or provide us with the charter as an additional submission. We will need this to be submitted ASAP.
4. We noticed that two versions of SAP (version **1**: 12/18/2015; version **3**: 6/17/2016) have been submitted to the Agency under IND 100996. However, in module 5 of NDA 208447, two versions of SAP with different dates (version **1**: 5/13/2016; version **2**: 5/18/2016) were submitted. Please clarify the discrepancy of SAP versions under IND 100996 and NDA 208447.

Please respond by no later than **COB, Wednesday November 16, 2016**. Please respond by 1) email to facilitate review 2) formal submission to the NDA.

Please confirm receipt of this email. If you have any questions please do not hesitate to ask.

Sincerely,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products

OND/CDER/FDA

Phone: 240-402-4978

Fax: 301-796-9845

Email: Jeannette.Dinin@fda.hhs.gov

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/s/

JEANNETTE L DININ
11/14/2016

From: Dinin, Jeannette
To: "[Chuck Miller](#)"
Subject: FDA Communication: NDA 208447/niraparib/QT study - IR/ Time Sensitive
Date: Tuesday, November 08, 2016 10:57:00 AM
Attachments: Highlights of ClinPharm and Cardiac Safety_20150923.doc
Importance: High

Hi Chuck,

In response to NDA 208447 we have the following information requests regarding your QT study:

1. In QTc Sub-study, patients were under intensive ECG monitoring and PK evaluation on CYCLE 1/DAY 1, but we cannot locate those data submitted. Please submit EG.XPT, ADEG.XPT, PC.XPT and ADPC.XPT, including the intensive monitoring period.
2. In the current EG/ADEG datasets, QT intervals were excluded, please make sure QT intervals are also in the new datasets.
3. Please submit all related digital ECG waveforms with annotations to the ECG warehouse (www.ecgwarehouse.com) for the QTc Sub-study.
4. Furthermore, provide the method the ECG central lab used to measure ECG intervals (manual, semi-automatic, or automatic), and what ECG readers were blinded to.

Additionally, please fill out the attached form. Please submit by **COB November 18, 2016**. If more time is needed for the ECG waveforms please contact me to let me know how much additional time would be needed for that part of the submission.

Please submit by 1) email to facilitate review 2) formal submission to the NDA with 356h.

Sincerely,

Jeannette Dinin

Regulatory Project Manager

Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products

OND/CDER/FDA

Phone: 240-402-4978

Fax: 301-796-9845

Email: Jeannette.Dinin@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	<p>Include maximum proposed clinical dosing regimen</p> <p>Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose</p> <p>Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen</p>	
Maximum tolerated dose	<p>Include if studied or NOAEL dose</p>	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events</p>	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	<p>Specify dosing regimen</p>	
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen</p>	
Metabolites	<p>Include listing of all metabolites and activity</p>	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p>	
Preclinical Cardiac Safety	<p>Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.</p>	
Clinical Cardiac Safety	<p>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</p>	

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/s/

JEANNETTE L DININ
11/08/2016



IND 100996

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

TESARO, Inc.
Attention: Chuck Miller
Vice President, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to your August 25, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that niraparib (MK-4827) for monotherapy maintenance treatment of adult patients with germline BRCA mutation (gBRCA) or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum based chemotherapy, meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of niraparib (MK-4827) for monotherapy maintenance treatment of adult patients with germline BRCA mutation (gBRCA) or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum based chemotherapy, to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When Breakthrough Therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial Breakthrough Therapy meeting².

We note your recent Pre-New Drug Application meeting held on September 21, 2016. At this point in your drug development program, holding this initial Breakthrough Therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the Breakthrough Therapy designation for niraparib (MK-4827) for monotherapy maintenance treatment of adult patients with germline BRCA mutation (gBRCA) or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum based chemotherapy, is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Jeannette Dinin, Regulatory Project Manager, at (240) 402-4978 or email Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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

/s/

GEOFFREY S KIM
10/14/2016

Benton, Sandra J

From: Benton, Sandra J
Sent: Thursday, September 29, 2016 8:01 AM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Smith, James P. (FDA/CDER); Maynard, Janet; LaVange, Lisa; Zineh, Issam
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Sharma, Khushboo; Wedlake, Lauren; Silva, Nicole; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Dinin, Jeannette; Robertson, Kim; Wedam, Suparna (FDA); Amiri Kordestani, Laleh (FDA); Ibrahim, Amna; Kim, Geoffrey
Subject: RE: October 12, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 100996

As the Council agrees with DOP1's recommendation to grant TESARO's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the October 12, 2016 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

From: Benton, Sandra J
Sent: Tuesday, September 20, 2016 12:22 PM
To: Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Smith, James P. (FDA/CDER); Maynard, Janet; LaVange, Lisa; Zineh, Issam
Cc: Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Sharma, Khushboo; Wedlake, Lauren; Silva, Nicole; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Dinin, Jeannette; Robertson, Kim; Wedam, Suparna (FDA); Amiri Kordestani, Laleh (FDA); Ibrahim, Amna; Kim, Geoffrey
Subject: October 12, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND 100996

Hi! OMP has scheduled a Medical Policy Council discussion on October 12, 2016 regarding the breakthrough therapy designation request from TESARO, Inc. for its IND 100996, Niraparib indicated as monotherapy maintenance treatment of adult patients with germline BRCA mutation (gBRCA) or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

DOP1 recommends that this breakthrough therapy request be granted. Attached is DOP1's background on the breakthrough therapy designation with its rationale for granting the request.

DOP1 has asked if this request can be reviewed by email.

Would you please review DOP1's recommendation and let me know by COB Friday, September 30 if –

- You agree with DOP1's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like to have a discussion of the development plan and what FDA will recommend, if appropriate.
- You disagree with DOP1's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: IND 100996 BTDR (3).doc >>

<< File: IND 100996 BTDR.PDF >>

APPEARS THIS WAY ON ORIGINAL

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 100996
Request Receipt Date	August 25, 2016
Product	Niraparib
Indication	Ovarian Cancer
Drug Class/Mechanism of Action	PARP inhibitor
Sponsor	TESARO, Inc.
ODE/Division	DOP1
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	October 24, 2016

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

“Niraparib is a poly (ADP-ribose) polymerase (PARP) ^{(b) (4)} inhibitor indicated as monotherapy maintenance treatment of adult patients with germline BRCA mutation (gBRCA) or homologous recombination deficiency (HRD)-positive platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.”

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? YES NO

3. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? YES NO
- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - Undetermined
 - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
 - i. Only animal/nonclinical data submitted as evidence
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)

¹ For a definition of serious and life threatening see Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Ovarian cancer is the fifth overall cause for cancer death in women, representing 5% of all cancer deaths in women. It is also the deadliest of gynecologic cancers: an estimated 14,240 deaths are expected in 2016 in the United States. Early stage ovarian cancer is often asymptomatic; therefore, it is often first detected in advanced stages when prognosis is poor. The 5-year overall survival rate of ovarian cancer patients is 46% across all stages, but only 29% in patients diagnosed with distant metastatic disease. Although platinum-based chemotherapy is effective at inducing an initial response, ovarian cancer will recur in the majority of women. Following a response to second line chemotherapy, most patients with platinum-sensitive disease do not receive treatment during the platinum-free interval as there is no FDA-approved therapy. This current standard of care is referred to as “watchful waiting,” that is, monitoring patients for disease progression and managing their symptoms. During the watch and wait period, ovarian cancer survivors report emotional problems, anxiety about cancer antigen (CA)-125 testing, and fear of recurrence. After relapse, patients respond moderately or poorly to subsequent chemotherapy, with later lines of therapy leading to progressively shorter platinum-free intervals.

Niraparib is an orally available, highly selective poly (ADP-ribose) polymerase (PARP)-1 and -2 inhibitor. Niraparib has also been evaluated in more than 30 ovarian cancer patient-derived xenografts (PDX) and tumor cell line xenograft models. Efficacy has been observed in breast

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

cancer (BRCA)1 and BRCA2 mutant xenografts and in homologous recombination (HR)-deficient wild-type BRCA models.

7. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor is using progression free survival (PFS) results from Study PR-30-5011-C (NOVA) to support this BTDR. PFS was the primary endpoint from this phase 3 study. PFS has been used previously by the FDA to grant regular approval for drugs used in the treatment of advanced ovarian cancer. There previously have been no approvals in the maintenance setting for advanced ovarian cancer.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

Clinical trial endpoints that have been used to support traditional approval of drugs used in the treatment of patients with advanced ovarian cancer include: ORR, PFS and OS.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None other than gBRCA and HRD status (discussed further in Section 10).

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no approved therapies for patients with advanced platinum-sensitive ovarian cancer following a response to second line chemotherapy. The standard of care in this situation is to monitor these patients and not administer anti-tumor therapy until they have progression of disease.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

None.

10. Information related to the preliminary clinical evidence:

The primary basis for this BTDR is Study PR-30-5011-C (NOVA), a randomized, placebo-controlled, phase 3 study in patients with recurrent, platinum sensitive high grade serous ovarian cancer who have either a germline BRCA mutation (gBRCAmut), or a tumor with high- grade serous or high- grade predominantly serous histology, but without a germline BRCA mutation(non-gBRCAmut).

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Major eligibility criteria for the NOVA study include:

- *Female patients*
- *>18 years of age*
- *Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and high grade (or Grade 3) serous or high grade predominantly serous histology or known to have gBRCAmut*
- *Received at least 2 platinum-based regimens, with the last regimen being platinum-based therapy.*
- *Had a response (CR or PR) to their last regimen.*
- *Have no measurable lesion >2 cm*
- *Normal cancer antigen 125 (CA-125) (or >90% decrease during the last platinum regimen which is stable for at least 7 days).*

Patients were enrolled into one of two independent cohorts based on germline BRCA mutation status (gBRCAmut and non-gBRCAmut). The non-gBRCAmut cohort included patients with homologous recombination deficiency (HRD)-positive tumors, including those with somatic BRCA mutations and other HR defects, and patients with HRD-negative tumors. Testing was performed at a central facility (Myriad Genetics, Salt Lake City, UT) using the myChoice® HRD test. Within each cohort, patients were randomized 2:1 to receive niraparib or placebo and were treated continuously with placebo or 300 milligrams of niraparib until progression, unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first. The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints include patient-reported outcomes, chemotherapy-free interval length, PFS2, overall survival, and other measures of safety and tolerability.

The primary analysis of PFS in both study cohorts was planned to occur when approximately 98 PFS events (based on a central review) were observed in the gBRCAmut cohort and also in the HRD-positive group within the non gBRCAmut cohort. The sample size was designed to test a hazard ratio (HR) of 0.5 for niraparib versus placebo. The study was designed to first test the primary PFS endpoint in the HRD-positive group, then if positive, test PFS for the entire non-gBRCA cohort in a hierarchical approach. Although an analysis was not prospectively defined for all patients in both cohorts combined, an exploratory analysis was performed, given the substantial treatment effect observed in each cohort independently.

As of the data cutoff of 30 May 2016, 103 events had been reported in the gBRCAmut cohort based on central independent review and 101 events had been reported in the HRD-positive non-gBRCAmut subset.

A total of 553 patients were randomized into this Phase 3 study at 107 centers worldwide. The study population comprises 203 patients randomized into the gBRCAmut cohort and 350 patients randomized into the non-gBRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumors that were defined as HRD-positive and 134 had tumors that were HRD-negative. HRD status was not determined for 54 patients as the test was inconclusive (n=26), the tumor sample was inadequate for testing (n=14) or the sample was missing (n=14). The non-gBRCAmut cohort analyses were based on the ITT population and included all patients, regardless of HRD status.

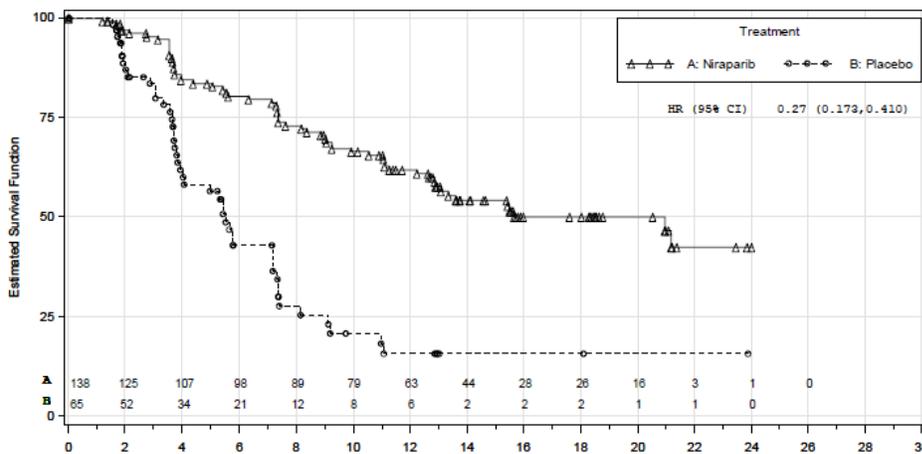
For all primary efficacy populations, median PFS was significantly longer for patients who received niraparib than for patients who received placebo:

- gBRCAmut cohort: 21.0 months versus 5.5 months (HR=0.27; 95% CI, 0.173 to 0.410); $p < 0.0001$)
- Non-gBRCA cohort
 - HRD-positive group: 12.9 months versus 3.8 months; (HR=0.38; 95% CI, 0.243 to 0.586; $p < 0.0001$)
 - HRD-negative group: 6.9 months versus 3.8 months; (HR=0.58; 95% CI, 0.361 to 0.922; $p < 0.0226$)
 - Overall cohort: 9.3 months versus 3.9 months; (HR=0.45; 95% CI, 0.338 to 0.607; $p < 0.0001$)

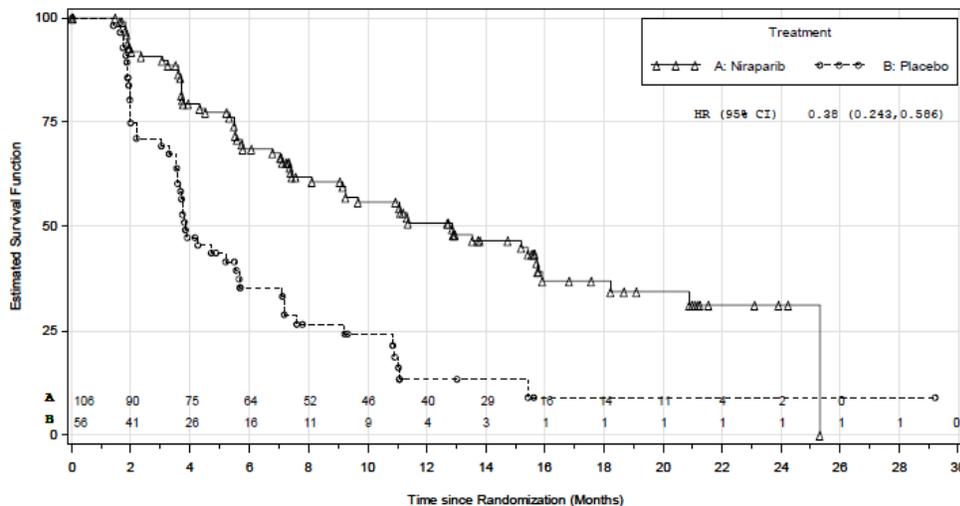
PFS was longer with niraparib (median 11.3 months versus 4.7 months, HR 0.38, 95% CI, 0.303, 0.488, $p < 0.0001$) in an exploratory pooled analysis that evaluated all patients in both cohorts combined.

Shown below are the Kaplan Meier curves for PFS in the various cohorts:

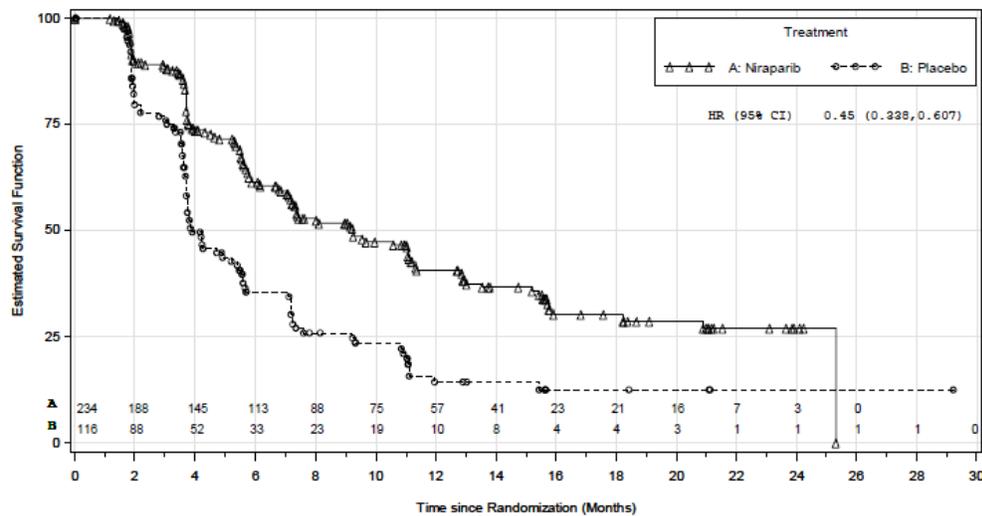
gBRCAmut Cohort (N=203)



Non-gBRCAmut Cohort, HRD-positive (N=162)



Non-gBRCAmut Cohort Overall (N=350)



Safety:

Most patients in both treatment groups experienced at least 1 treated emergent adverse event (TEAE), including all 367 patients who received niraparib and 171 of 179 (96%) patients who received placebo. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 TEAEs (74% versus 23%), serious adverse events (SAEs) (30% versus 15%), TEAEs leading to treatment interruption (69% versus 5%), TEAEs leading to dose reduction (67% versus 15%), and of TEAEs leading to treatment discontinuation (15% versus 2%) were higher for niraparib. There were no on-treatment deaths reported during the study. The most commonly observed non-hematologic side effects (all grades) observed in niraparib compared to placebo-treated patients were nausea (74% versus 35%), fatigue (46% versus 32%), constipation (40% versus 20.0%), and vomiting (34% versus 16%). Greater than 85% of the AEs reported were \leq Grade 2. The most commonly observed hematologic side effects (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), and neutropenia (18%). The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received niraparib (5 of 367; 1.4%) was similar to those in patients who received placebo (2 of 179; 1.1%).

11. Division's recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

We recommend granting Breakthrough Designation for niraparib as monotherapy maintenance treatment for platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy in the following populations:

- 1. Patients with gBRCA mutation*
- 2. Patients with non-gBRCA mutation/HRD positive*

We do not recommend extending the Breakthrough Designation to patients with non-gBRCA mutation/HRD negative recurrent ovarian, fallopian tube, or primary peritoneal cancer.

Patients with recurrent, platinum sensitive, ovarian, fallopian tube, or primary peritoneal cancer are not cured with currently available therapy and represent an ongoing medical need. The development of

treatment to prolong a patient's response to platinum-based chemotherapy will extend the time to the next treatment phase and may delay the toxicities associated with therapy. Currently, there are no approved therapies in the maintenance setting for patients with advanced platinum-sensitive ovarian cancer following a response to second line chemotherapy. Preliminary data provided by the Sponsor from the NOVA study showed a statistically significant improvement in the median PFS for the niraparib treatment arm versus the placebo arm in gBRCAmut cohort, non-gBRCAmut/HRD-positive cohort and the overall non-gBRCAmut cohort. As discussed at the ODAC meeting in June 2014 discussing the olaparib NDA, a greater than 6 month improvement in median PFS in the maintenance setting with an acceptable safety profile would likely be considered clinically meaningful. Therefore, the improvement in median PFS by 15.5 months in the gBRCAmut cohort and by 9.1 months in the non-gBRCAmut/HRD-positive group would be considered clinically meaningful. In addition, preliminary data reveal that niraparib is associated with an acceptable safety profile.

DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor is planning to submit a NDA for niraparib based on the results from the NOVA study. A pre-NDA meeting with the Agency has been scheduled for September 21, 2016.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Cancer Facts and Figures 2016. American Cancer Society.

<http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf>

SEER Stat Fact Sheets: Ovarian Cancer. National Cancer Institute.

<http://seer.cancer.gov/statfacts/html/ovary.html>.

Ferrell B, Smith SL, Cullinane CA, Melancon C. Psychological wellbeing and quality of life in ovarian cancer survivors. Cancer. 2003;98(5):1061-1071.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

APPEARS THIS WAY ON ORIGINAL

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

/s/

SANDRA J BENTON
09/29/2016

GEOFFREY S KIM
09/29/2016



IND 100996

MEETING MINUTES

TESARO, Inc.
Attention: Chuck Miller
Vice President, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to the meeting between representatives of your firm and the FDA on September 21, 2016. The purpose of the meeting was to discuss your plans to submit an NDA by the end of October 2016 for use of niraparib as maintenance treatment in patients with platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy based on the pivotal phase 3 trial in ovarian cancer (PR-30-5011-C /NOVA).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 21, 2016; 2:00-3:00 pm
Meeting Location: White Oak, Building 22; Room 1311

Application Number: 100996
Product Name: niraparib (MK-4827)
Indication: Ovarian cancer
Sponsor/Applicant Name: TESARO, Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Geoffrey Kim, MD, Director, Division of Oncology Products 1
Laleh Amiri-Kordestani, Clinical Team Leader, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
Tiffany Ricks, PhD, Pharmacology/Toxicology Reviewer, DHOT
Wimolnut Manheng, PhD, Pharmacology/Toxicology Reviewer, DHOT
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Zhang Hui, PhD, Biometrics Reviewer, DBV
Xiao-Hong Chen, PhD, Pharmaceutical Assessment Lead, ONDP
Elsbeth Chikhale, PhD, Acting Biopharmaceutics Lead, ONDP
Kaushalkumar Dave, PhD, Biopharmaceutics Reviewer, ONDP
Hisani Madison, PhD, MPH, Regulatory Scientist, CDRH/OIR/DMGP
Reena Philip, PhD, Division Director, CDRH/OIR/DMGP
Roseane Charlab Orbach, PhD, Genomics Team Leader, DCP V
Jeannette O'Donnell, Regulatory Project Manager, DOP1

FDA ATTENDEES BY PHONE

Janine Stewart, PharmD, Safety Evaluator, OMEPRM
Neil Vora, PharmD, MBA, Safety Regulatory Project Manager, OMEPRM

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Shefali Agarwal, MD, MPH Senior Medical Director, Clinical Science TESARO

Mary Lynne Hedley, PhD, President, Chief Operating Officer, TESARO

Martin Huber, MD, SVP, Chief Medical Officer, TESARO

Jennifer Jackson, PhD, SVP, Global Regulatory Affairs and Quality Assurance, TESARO

Vikram Kansra, PhD, VP, Clinical Pharmacology and Drug Disposition, TESARO

Dave Lust, MS, Exec. Director, Regulatory CMC, TESARO

Chuck Miller, VP, Regulatory Affairs, TESARO

Lene Rose Arfelt MS, VP, Regulatory International, TESARO

(b) (4)

Eric Pratts, SVP, Quality, Compliance, and Regulatory Affairs, Myriad Genetics

(b) (4)

1.0 BACKGROUND

Niraparib is a poly (ADP-ribose) polymerase (PARP)^{(b) (4)} inhibitor indicated as monotherapy maintenance treatment of adult patients with platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.

Niraparib is an orally available poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) - 1 and -2 inhibitor. The primary basis for the proposed NDA is Study PR-30-5011-C (NOVA), a double-blind, 2:1 randomized, placebo-controlled phase 3 study in patients with recurrent, platinum sensitive, high grade, serous ovarian cancer, who have either a germline BRCA mutation (gBRCAmut), or a tumor with high- grade serous or high-grade predominantly serous histology, but without a germline BRCA mutation (non-gBRCAmut).

Major eligibility criteria for the NOVA study include:

- female patients
- >18 years of age
- histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and high grade (or Grade 3) serous or high grade predominantly serous histology or known to have gBRCAmut
- Received at least 2 platinum-based regimens, with the last regimen being platinum-based therapy
- Had a response (CR or PR) to their last regimen.
- Have no measurable lesion >2 cm
- Normal cancer antigen 125 (CA-125) (or >90% decrease during the last platinum regimen which is stable for at least 7 days)

Patients were enrolled into one of two independent cohorts based on germline BRCA mutation status. One cohort enrolled patients who were germline BRCA mutation carriers (gBRCAmut), and the second cohort enrolled patients who were not germline BRCA mutation carriers (non-

gBRCAmut). The non-gBRCAmut cohort included patients with HRD-positive tumors, including those with somatic BRCA mutations and other HR defects, and patients with HRD-negative tumors. Within each cohort, patients were randomized 2:1 to receive niraparib or placebo and were treated continuously with placebo or 300 milligrams of niraparib until progression, unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first. The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints include patient-reported outcomes, chemotherapy-free interval length, PFS2, overall survival, and other measures of safety and tolerability.

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As of the data cutoff of May 30, 2016, 103 events had been reported in the gBRCAmut cohort based on central independent review and 101 events had been reported in the HRD-positive non-gBRCAmut subset.

A total of 553 patients were randomized into this phase 3 study at 107 centers worldwide. The study population comprises 203 patients randomized into the gBRCAmut cohort and 350 patients randomized into the non-gBRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumors that were defined as HRD-positive and 134 had tumors that were HRD-negative. HRD status was not determined for 54 patients as the test was inconclusive (n=26), the tumor sample was inadequate for testing (n=14) or the sample was missing (n=14). The non-gBRCAmut cohort analyses were based on the ITT population and included all patients, regardless of HRD status.

For all primary efficacy populations, median PFS was significantly longer for patients who received niraparib than for patients who received placebo:

- gBRCAmut cohort: 21.0 months versus 5.5 months (HR, 0.27; 95% CI, 0.173 to 0.410); p<0.0001)
- Non-gBRCA cohort
 - HRD-positive group: 12.9 months versus 3.8 months; (HR, 0.38; 95% CI, 0.243 to 0.586; p<0.0001)
 - Overall cohort: 9.3 months versus 3.9 months; (HR, 0.45; 95% CI, 0.338 to 0.607; p<0.0001)

PFS was longer with niraparib (median 11.3 months versus 4.7 months, HR 0.38, 95% CI, 0.303, 0.488, p<0.0001) in an exploratory pooled analysis that evaluated all patients in both cohorts combined.

Most patients in both treatment groups experienced at least 1 TEAE, including all 367 patients who received niraparib and 171 of 179 (96%) patients who received placebo. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 TEAEs (74% versus 23%), serious adverse events (SAEs) (30% versus 15%), TEAEs leading to treatment interruption (69% versus 5%), TEAEs leading to dose reduction (67% versus 15%), and of TEAEs leading to treatment discontinuation (15% versus 2%) were higher for niraparib. There were no on-treatment deaths reported during the study. The most commonly observed non-hematologic side effects (all grades) observed in niraparib compared to placebo-treated patients were nausea (74% versus 35%), fatigue (46% versus 32%), constipation (40% versus 20.0%), and vomiting (34% versus 16%). Greater than 85% of the AEs reported were \leq Grade 2. The most commonly observed hematologic side effects (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), and neutropenia (18%). The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received niraparib (5 of 367; 1.4%) was similar to that in patients who received placebo (2 of 179; 1.1%).

FDA sent Preliminary Comments to TESARO on September 16, 2016.

2. DISCUSSION

- 1) Does the Division agree that the results from the Phase 1 study, the AME study, and the Pivotal study NOVA (which included FE and QTc substudies) would support the filing and review of niraparib for an ovarian cancer indication?

FDA Response: Yes.

- 2) Does the Division agree that the myChoice[®] HRD test might provide useful information for physicians and patients and should be available as a complementary diagnostic?

FDA Response: Yes.

The device manufacturer should also prepare a supplement for the BRACAnalysis CDx.

TESARO Response (submitted September 20, 2016): TESARO would like to discuss the timing of the ^{(b) (4)} BRACAnalysis supplement in relation to the NDA.

Meeting Discussion: The FDA agreed that CDER and CDRH will work together ^{(b) (4)}

Details of the timeline to be discussed further.

APPEARS THIS WAY ON ORIGINAL

- 3) Does the Division agree with the Sponsor's assessment that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary for niraparib?

FDA Response: At this time, a REMS does not appear necessary; however, this will be a review issue.

- 4) Does the Division agree with the proposed scope (contents and data cut-off) of the 4-month Safety Update and does the Division have a preferred timing relative to the submission of the final reviewable unit of the niraparib NDA?

FDA Response: The proposed contents and data cut-off dates are adequate. Your 120 day safety update may be submitted on day 90.

- 5) Does the Division agree with the Sponsor's proposal for submission of minor components within 30 days of submission?

FDA Response: Yes. Your approach appears to be reasonable. However, we expect 12 months of stability data for each of three registration batches at the time of the NDA submission, per ICH Q1A. You may submit additional stability data within 30 days of your NDA submission. If you have less than 12 months long term stability data for three primary stability batches at 30 days of NDA submission, it may impact the shelf life of your drug product.

TESARO Response (submitted September 21, 2016): In addition to the above, TESARO would like to seek the Division's agreement with the submission of items l, m, n as additional late components.

Meeting Discussion: FDA agreed that within 30 days of the completion of the rolling submission of the NDA, the b, i, l, m, and n from the biopharmaceutics additional comments section of this document, will be submitted. This will include the n=12 data as well as the 12 month stability data.

- 6) Can the Division please comment on the likely need for, or potential topics for discussion at, an Oncologic Drugs Advisory Committee (ODAC) for niraparib for the proposed indication?

FDA Response: This will be a review issue.

- 7) To facilitate the review of the NDA, TESARO proposes an Applicant Orientation Meeting with the Division within 30 days of submission of the NDA. Does the Division agree?

FDA Response: The Division will attempt to schedule an Applicant Orientation Meeting within 30 days of the receipt of the final component of the NDA.

- 8) Given the global nature of the Phase 3 pivotal trial, would the Agency comment on the potential timing of clinical trial site as well as Sponsor inspections?

FDA Response: No. The decision to conduct clinical site inspections is an application review issue. The timing of the anticipated clinical trial site or sponsor inspections would be determined during the review of the application.

ADDITIONAL FDA COMMENTS

Biopharmaceutics:

FDA has the following general comments regarding the dissolution information that should be provided in the original NDA submission.

Dissolution Method: Include the dissolution method development report supporting the selection of the proposed dissolution test. Include the following information in the dissolution method development report:

- a. Solubility data for the drug substance over the physiologic pH range.
- b. Detailed description of the dissolution test being proposed for the evaluation of the product and the developmental parameters (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for the product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions used for each test. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45 60, 90 and 120 min.

Meeting Discussion: FDA Agreed that the submission of n=6 dissolution data is acceptable with regards to the dissolution method development report and continuous stability testing. In order for FDA to evaluate the dissolution method acceptance criteria FDA requests n=12 data for the clinical batch and registration batch. Those registration and clinical batches were originally tested at n=6.

- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the product. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).
- d. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes and critical process parameters (i.e., ± 10 -20% change to the specification-ranges of these variables).

- e. Provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
- f. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.

Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion (a) of the product, consider the following points:

- g. FDA recommends use of the dissolution profile data (i.e., 15, 20, 30, 45, and 60 min) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) for setting the dissolution acceptance criterion (a).
- h. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.
- i. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).
- j. The selection of the specification time point should be where Q=80 % dissolution occurs.
- k. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the CTD.

Data Presentation: In the dissolution method development report, present detailed experimental data as follows:

- l. Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
- m. In addition to the mean dissolution data presented in graphical and tabular formats in the dissolution method development report, submit all individual vessel dissolution data for the clinical and registration/stability batches in “.xpt” format. Submit a DEFINE file along with the .xpt files.
- n. Present batch release and stability dissolution data graphically; in the plot(s) of individual vessel data for the clinical and stability batches, include data at release, zero stability time point, and over the duration of stability testing under long-term storage conditions.

Meeting Discussion: The sponsor noted that the submission of l, m, n will be submitted in section 3.2.r. FDA agreed to this approach and requested that reference to this location will be made in 3.2.p.2. and in the Reviewer Guide.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that while at this time a REMS does not appear necessary, the final determination will be a review issue.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.
- **NDA 208447: CLINICAL DATA – MODULE 5**
 - **A portion of Module 5 (Clinical data) will be submitted in mid-October 2016 as “clinical information, pre-submission.” The remainder of Module 5 will be submitted to the NDA at the end of October 2016 at which time the PDUFA clock will start.**
- We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
- **NDA 208447: LATE COMPONENT - QUALITY**
 - **We expect 12 months of stability data for each of three registration batches at the time of the NDA submission, per ICH Q1A. You may submit additional stability data within 30 days of your NDA submission. If you have less than 12 months long term stability data for three primary stability batches at 30 days of NDA submission, it may impact the shelf life of your drug product.**
- **NDA 208447: LATE COMPONENT – BIOPHARMACEUTICS**
 - **Within 30 days of the completion of the rolling submission of the NDA, the b, i, l, m, and n from the biopharmaceutics additional comments section of this document, will be submitted. This will include the n=12 data as well as the 12 month stability data.**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1.

Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing (Establishment function)
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email Address
1.				
2.				

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

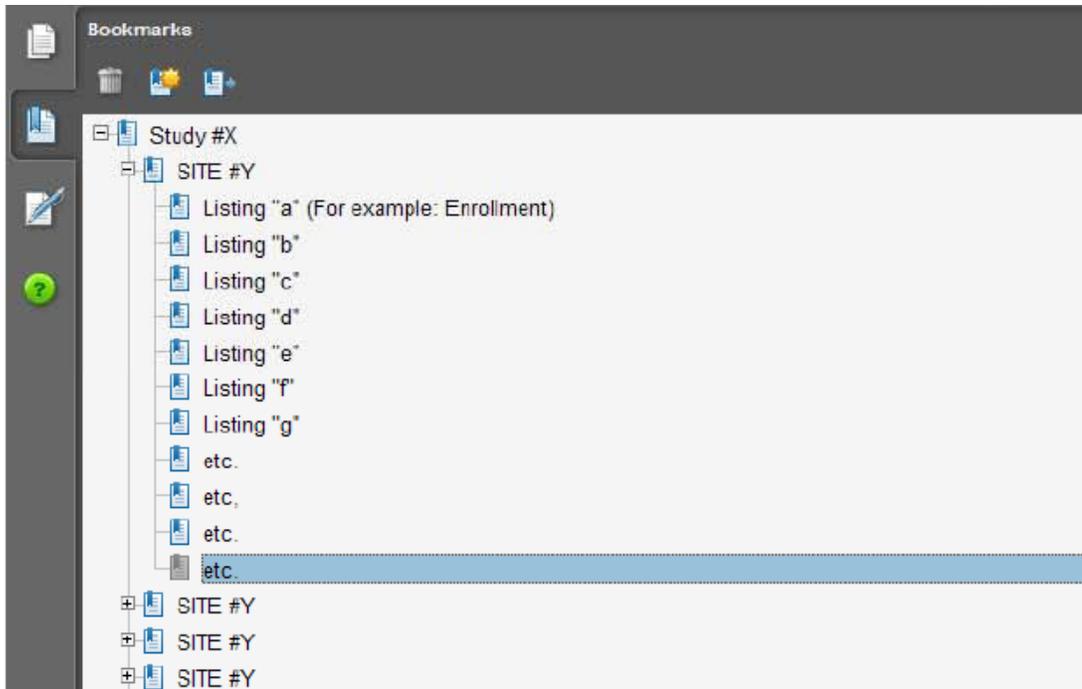
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records,

- IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry “*Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning*” (available at the following link: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

APPEARS THIS WAY ON ORIGINAL

Attachment 1

**Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For Items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for Items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1:
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page:
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached slides

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JEANNETTE L DININ
09/29/2016

LALEH AMIRI KORDESTANI
09/29/2016



IND 100996

GRANT FAST TRACK ROLLING REVIEW

TESARO, Inc.
Attention: Chuck Miller
Vice President, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to your August 1, 2016, request for Fast Track designation. We have reviewed your request and conclude that the required criteria have been met and are designating as a Fast Track development program the investigation of niraparib (MK-4827) for the treatment of patients with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. We have also reviewed your request for submission of portions for review of your planned marketing application and find it acceptable.

If you pursue a clinical development program that does not support use of niraparib (MK-4827) for the treatment of patients with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal, the application will not be reviewed under the Fast Track drug development program and submission of sections of the marketing application will not be accepted under this program. For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics"¹. This document may be requested from the Office of Communications, Division of Drug Information at 301-796-3400 or 1-888-463-6332.

If you have any questions, contact Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GEOFFREY S KIM
09/07/2016



IND 100996

**MEETING REQUEST-
WRITTEN RESPONSES**

TESARO, Inc.
Attention: Chuck Miller
Vice President, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to your submission dated April 26, 2016, containing a Type C meeting request. The purpose of the requested meeting was to discuss topics on the proposed clinical content and format of a planned NDA and gain Division agreement.

Further reference is made to our Meeting Granted letter dated May 18, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 9, 2016 background package.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: 100996
Product Name: niraparib (MK-4827)
Indication: (b) (4) Ovarian cancer
Sponsor/Applicant Name: TESARIO, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND)

TESARO has requested a Type C meeting to obtain FDA guidance on selected topics related to the clinical content and format of a planned NDA in advance of a pre-NDA meeting for the following indication:

Niraparib is indicated as maintenance treatment in patients with recurrent, platinum sensitive high grade serous ovarian cancer who are BRCA mutation positive or homologous recombination deficient (HRD) positive as detected by an FDA approved test.

Niraparib is an orally available poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) - 1 and -2 inhibitor. To date, approximately 1200 patients have been enrolled in studies with niraparib (158 in phase 1; 305 in phase 2; 737 in phase 3).

The primary basis for the proposed NDA is Study PR-30-5011-C (NOVA), a double-blind, 2:1 randomized, placebo-controlled phase 3 study in patients with recurrent, platinum sensitive high grade serous ovarian cancer who have either a germline BRCA mutation (gBRCAmut), or a tumor with high- grade serous or high- grade predominantly serous histology, but without a germline BRCA mutation(non-gBRCAmut). NOVA is an ongoing study which was closed to enrollment as of June 1, 2015.

Major eligibility criteria for the NOVA study include:

- female patients
- ≥ 18 years of age
- histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and high grade (or Grade 3) serous or high grade predominantly serous histology or known to have gBRCAmut
- Received at least 2 platinum-based regimens, with the last regimen being platinum-based therapy.
- Had a response (CR or PR) to their last regimen.

- Have no measurable lesion >2 cm
- Normal cancer antigen 125 (CA-125) (or >90% decrease during the last platinum regimen which is stable for at least 7 days).

In this study, eligible patients are randomized in a 2:1 ratio to receive niraparib or matching placebo capsules, administered orally QD continuously every cycle (28 days) until disease progression, unacceptable toxicity, death, withdrawal of consent, or lost to follow-up, whichever comes first.

The primary objective of this study is to evaluate efficacy of niraparib as maintenance treatment in patients who have recurrent, platinum sensitive ovarian cancer as assessed by the prolongation of PFS. This objective will be independently evaluated in the gBRCAmut and non-gBRCAmut cohorts. The statistical analysis of the primary endpoint of PFS for the non-gBRCAmut cohort in the NOVA study will be performed in a hierarchical manner, with a test for the HRD positive subset performed first, followed by a test of the overall population in the non-gBRCAmut cohort if the first test is statistically significant.

The NOVA intent-to-treat (ITT) population, defined as all randomized patients even if no study drug was ingested, consists of 570 patients who were randomized to niraparib or placebo. The primary analysis of PFS was planned based on 100 PFS events in the gBRCAmut cohort (assumes 180 gBRCAmut patients) and 98 PFS events non-gBRCAmut cohort (assumes 310 non-gBRCAmut patients). The Sponsor anticipates this event rate to be achieved in the summer of 2016.

An overview of the content for the proposed NDA is shown in the following table:

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Indication	Protocol Number	Study Descriptor ¹	Accrual Status	CSR included in Module 5	Included in SCS (ISS)	Included in SCE (ISE)
Advanced Solid Tumors and/or Hem Malignancies	PN001 ²	Ph1, OL, dose escalation (N=104)	Closed	Full CSR	Yes	Yes
	(b) (4)					
	PR-30-5015-C (ADME)	Ph1, OL, ADME study (N=12)	Closed	Full CSR	Yes (Not integrated)	No
High Grade Serious Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer	PR-30-5020-C (QUADRA)	Ph2, OL in adv, relapsed, high grade serious epithelial ovarian, fallopian, or primary peritoneal cancer w/3+ prior therapies (N=305)	Enrolling	Synopsis only	Yes	No
	PR-30-5011-C (NOVA)	Ph3, R, DB, placebo-controlled, maintenance therapy in platinum sensitive high grade serious epithelial ovarian, fallopian, or primary peritoneal cancer w/2 prior platinum-based lines (N=570) ⁴	Closed	Full CSR	Yes	Yes
	NOVA QTc Substudy	QTc substudy (N=26)	Closed	Full CSR	Yes	No
	NOVA FE Substudy	FE substudy (N=18) ⁵	Closed	Full CSR	Yes	No
(b) (4)						

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; CSR = clinical study report; DB=double-blind; FE=food effect; OL=open-label; R=randomized; SoC=standard of care; TMZ=temozolomide

¹ Approximate number enrolled to date

² Expansion cohort included 50 patients with ovarian or peritoneal cancer

³ (b) (4)

⁴ NOVA enrollment number includes all 18 patients in Food Effect Substudy; 15 patients in NOVA main study also had QTc evaluations

⁵ All patients in Food Effect Substudy had QTc evaluations

2.0 QUESTIONS AND RESPONSES

Clinical

Question 1

Does the Division agree with the proposed content for the Summary of Clinical Efficacy and that it could fulfill the requirements for the Integrated Summary of Effectiveness for the upcoming niraparib NDA?

FDA RESPONSE: Yes.

Question 2

Does the Division agree with the Sponsor's proposal to provide the text portion of the Integrated Summary of Safety in Module 2.7.4 as the Summary of Clinical Safety with supporting appendices and datasets in Module 5.3.5.3 for the upcoming niraparib NDA?

FDA RESPONSE: Yes.

Question 3

Does the Division agree with the proposed content for the Summary of Clinical Safety and Integrated Summary of Safety for the upcoming niraparib NDA?

FDA RESPONSE: Yes.

Question 4

Does the Division agree with the Sponsor's proposed plan for individual patient narratives for the upcoming niraparib NDA?

FDA RESPONSE: No. Please also provide patient narratives for all SAEs (not only treatment-emergent) and for all deaths due to progression of disease.

Question 5

Does the Division agree with the Sponsor's proposal regarding inclusion of case report forms in the upcoming niraparib NDA?

FDA RESPONSE: No. Please provide case report forms for all patients.

Question 6

The Sponsor considers the pivotal Phase 3 NOVA study in ovarian cancer to be the only covered clinical study for the purpose of compliance with CFR Title 21 Part 54. Does the Division agree with this assessment?

FDA RESPONSE: Yes.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

APPEARS THIS WAY ON ORIGINAL

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/s/

LALEH AMIRI KORDESTANI
07/14/2016



IND 100996

MEETING MINUTES

TESARO, Inc.
Attention: Kathleen Andrade
Senior Manager Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Andrade:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to the meeting between representatives of your firm and the FDA on March 30, 2015. The purpose of the meeting was to discuss your clinical development plan in ovarian cancer and to discuss options for approval in the ovarian cancer setting in specific patient populations (maintenance setting for patients who have platinum sensitive ovarian cancer, (b) (4) as well as in patients with advanced ovarian cancer who have had 3 or more prior therapies).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

APPEARS THIS WAY ON ORIGINAL

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products 1
Center for Drug Evaluation and Research

Amy McKee, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products 1
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: March 30, 2015; 2:00pm EST
Meeting Location: W.O. Bldg. #22; Conf. Room 1421

Application Number: 100996
Product Name: Niraparib (MK-4827)
Indication: Ovarian cancer
Sponsor/Applicant Name: TESARO, Inc.

Meeting Chair: Amy McKee, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Geoffrey Kim, M.D., Director, DOP1
Amna Ibrahim, M.D., Deputy Director, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Suparna Wedam, M.D., Clinical Reviewer, DOP1
Hui Zhang, Ph.D., Biometrics Reviewer, DBV
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV
Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer, DCP5
Jeanne Fourie-Zirkelbach, Ph.D., Acting Clinical Pharmacology Team Leader, DCP5
Rosane Charlab-Orbach, Ph.D., Genomics Reviewer, DCP5
Todd Palmby, Ph.D., Non-Clinical Team Leader, DHOT
Gwynn Ison, M.D., Clinical Reviewer, DOP1
Sanjeeve Balasubramaniam, M.D., Clinical Reviewer, DOP1
Reena Philip, Ph.D., Director, CDRH, DMGP
Eunice Lee, Ph.D., CDRH Reviewer, DMGP
Stephanie Donahoe, Regulatory Health Project Manager, OGD
Kim J. Robertson, Regulatory Health Project Manager, DOP1

TESARO, Inc. ATTENDEES

Tanya Lewis, M.S., Vice President, Regulatory Affairs (via phone)
Andrew Henderson, M.B.A., Director, Regulatory Affairs
Shefali Agarwal, M.D., Senior Medical Director
Robert Martell, M.D., Chief Medical Officer
Mary Lynne Hedley, Ph.D., President and COO of TESARO, Inc.

TESARO, Inc. ATTENDEES (cont.)

(b) (4)

Vikram Kansra, CPDD, Vice President, Clinical Pharmacology
Zhi-Yi Zhang, Ph.D., Director, Clinical Pharmacology and Drug Disposition
Matthew McLeod, Senior Director, Portfolio Management
Alexander Gutin, Ph.D., Senior Vice President, Bioinformatics, Myriad Genetics, Inc.
Bradley J. Monk, M.D., F.A.C.O.G., F.A.C.S.
Kathy Andrade, Senior Manager Regulatory Affairs

1.0 BACKGROUND

TESARO is conducting a global phase 3 study, PR-30-5011 entitled, “A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer” (NOVA study). Niraparib is a potent and selective poly (ADP-ribose) polymerase (PARP) inhibitor that is activated by binding to DNA double or single strand breaks. PARP inhibitors may be ideal for treating individuals with tumors bearing mutations in DNA repair pathways, including those with germline BRCA mutations (gBRCAmut) who develop ovarian cancer.

The primary objective of the NOVA study is to evaluate efficacy of niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer as assessed by the prolongation of progression-free survival (PFS). This objective will be independently evaluated in a cohort of patients with germline BRCA mutation (gBRCAmut) and in a cohort of patients who have high grade serous or high grade predominantly serous histology but without such gBRCA mutations (non-gBRCAmut). Patients in the non-gBRCAmut cohort have been reported to share distinctive DNA repair defects with gBRCAmut carriers, a phenomenon broadly described as “BRCAness”. Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. As a result, the original protocol was modified to prospectively identify a test for HRD as the tumor biomarker classifier to be evaluated in the non-gBRCAmut cohort.

In addition to the NOVA study, TESARO also plans to conduct an open label phase 2 study in patients with advanced ovarian cancer who have received 3 or more prior lines of therapy. In this study objective response rate and duration of response will be evaluated. The rationale for this study are data from a phase1/2 study in which there was a 75% response rate and in patients receiving niraparib a duration of response of greater than 15 months was observed.

(b) (4)

TESARO would like to discuss with the Agency options for obtaining approval in the ovarian cancer setting in the various patient populations described above.

FDA sent Preliminary Comments to TESARO, Inc. on March 27, 2015.

2. DISCUSSION

1. Sponsor Question 1

Does the Agency agree that HRD positive patients are an identifiable patient population for which labeling could be defined?

FDA RESPONSE: No, it is unclear whether you are defining the HRD+ population as independent from those patients with either germline or somatic BRCA mutation. At this point, there is insufficient evidence to determine whether there may be a differential response to niraparib in the patient population with gBRCA mutation vs tBRCA vs genomic instability. This may lead to difficulties in interpreting the results of your trials, as one group may drive the results of the trial. In addition, (b) (4)

Meeting Discussion: The Sponsor clarified the testing procedure and populations proposed. The Sponsor will provide an amended statistical analysis for review to address the subset analysis.

2. Sponsor Question 2

Does the Agency agree that the pre-specified primary endpoint in the non-gBRCA^{mut} cohort as described in the NOVA protocol and SAP could support approval of niraparib in patients whose tumors are HRD positive as defined by the MyChoice HRD test?

FDA RESPONSE: The agency reiterates comments dated January 21, 2015 (SN0217). Ovarian cancer can be very difficult to assess radiographically, and a statistically significant difference in PFS may not demonstrate a clinically meaningful difference. Therefore, you will need to demonstrate a large difference in PFS between arms. Please also note that for both the gBRCA_m cohort and non-gBRCA_m cohort, the trial may be overpowered and detect a small PFS difference. We refer you to the ODAC discussion held on June 25, 2014, regarding the magnitude of PFS benefit that is needed in the maintenance setting in ovarian cancer.

As for your SAP, we are concerned about the timing of the analyses in the sub-study for the non-gBRCA_{mut} cohort. In your responses to the Agency's comments dated March 2, 2015 (SN0217), you stated that "Based on the current rates of trial enrollment, it is anticipated that the required number of PFS events for the HRD+ subset will occur approximately 8 months after the required events for the entire cohort. The timing of the PFS analyses is based on the timing of the occurrence of events. We also note that the treatment blinding will be maintained until the required events are available for analysis." You should conduct the analyses for the non-gBRCA_{mut}/HRD-positive sub-cohort, the non-gBRCA_{mut}/HRD-negative cohort, and the entire non-gBRCA cohort at the same time, i.e., after observing 98 PFS events in the HRD-positive subcohort or 140 PFS events in the non-gBRCA_{mut} cohort, whichever occurs later.

We note that, as defined, the HRD+ population/non-gBRCA_{mut} cohort will contain both sBRCA_{mut} and genomic instability. The results should be consistent in both sub-groups to make a marketing claim for this sub-population.

Meeting Discussion: For all clinical trials assessing the activity of PARP inhibitors in molecularly defined patient populations, the Agency recommends that, at the very least, the Sponsor pre-specify the analyses for the gBRCA_m population and for the sBRCA_m + HRD population. Preferably, the Sponsor will pre-specify the analyses in each of these populations separately and include a plan to control type-I error.

From the data that the Sponsor provided regarding the sBRCA_m population enrolled to the NOVA study, it appears that the numbers in this population will be low. In this case, the Agency acknowledges the rationale for not including a formal analysis of efficacy in this population. The Sponsor plans to conduct this as a descriptive analysis and will modify the SAP accordingly.

3. Sponsor Question 3

Does the Agency agree that a clinically meaningful improvement in PFS supported by no decrement in overall survival (b) (4)?

FDA RESPONSE:

(b) (4)

(b) (4)

4. Sponsor Question 4

Does the Agency agree (b) (4)?

FDA RESPONSE: See our response to Question #1.

Meeting Discussion: No further discussions were necessary.

5. Sponsor Question 5

Assuming an acceptable patient safety profile, does the Agency agree that clinically meaningful and durable disease response rates an objective response rate (CR+PR as defined by RECIST version 1.1) would be acceptable for accelerated approval in the advanced ovarian cancer setting (three or more lines of prior therapy)?

FDA RESPONSE: This may be acceptable for accelerated approval depending on the regulatory landscape at the time of submission. In addition, approval for the entire population would not be granted if the results are solely driven by the HRD+/gBRCA_{mut}+ subset.

Meeting Discussion: No further discussions were necessary.

6. Sponsor Question 6

If the Agency agrees that a clinically meaningful and durable disease response would be acceptable for accelerated approval in the advanced ovarian cancer setting, would the Agency accept the NOVA study as the confirmatory study?

FDA RESPONSE: This may be acceptable. This would be a review issue based on the risk/benefit profile. See our response to Question #2.

Meeting Discussion: No discussions were necessary.

Additional Comment:

Please provide information regarding the incidence of MDS/AML with niraparib in your clinical development program to date.

Meeting Discussion: The Sponsor provided data regarding the incidence of MDS/AML in its database.

Based on the Agency's current understanding of the science surrounding the development of PARP inhibitors in patients with BRCA mutations and deficiencies in homologous repair, we recommend the following guidelines when describing the various types of potential patient populations to be studied in clinical trials with PARP inhibitors:

- gBRCAM – deleterious or suspected deleterious germline BRCA mutation.
- tBRCAM or sBRCAM – (tumor or somatic) deleterious or suspected deleterious BRCA mutation found in tumor specimens in the absence of gBRCAM.
- HRD – homologous recombination deficiency in the setting of the absence of either gBRCAM or t/sBRCAM.

Meeting Discussion: No further discussions were necessary.

ADDITIONAL MEETING DISCUSSION:

The Sponsor asked about possible Breakthrough Therapy Designation (BTD) based upon data from 10 patients. The Agency responded that the Sponsor should reconsider BTD when they have data from more patients.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

(Sponsor slides attached)

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/s/

KIM J ROBERTSON
04/15/2015

AMY E MCKEE
04/20/2015



IND 100996

ADVICE/INFORMATION REQUEST

TESARO, Inc.
Attention: Kathleen Andrade
Senior Manager Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Andrade:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to your amendment dated November 26, 2014, containing a request for written feedback, as it pertained to TESARO, Inc.'s plan for clinical pharmacology development.

We have the following comments and recommendations with regard to your questions:

Question 1:

Does the FDA Agree that the Conducted and Planned Clinical Pharmacology Studies for Niraparib are Appropriate and Sufficient to Support Registration?

FDA:

Your overall clinical pharmacology development plan appears acceptable. However, please see the response to Question 2.

Question 2:

Does the FDA Agree with the Proposed Population PK and E-R Analyses Plans?

FDA:

In general, your proposed population PK and E-R analysis plans appear acceptable; however you should adequately address the following issues:

1. Your proposed population PK approach using phase 1 and 3 data can be useful to assess the impact of renal or hepatic impairment on niraparib PK. We recommend that you enroll a sufficient number of patients with a wide range of hepatic and renal function in the trials and get enough PK samples from each patient to characterize their PK. You should pre-plan the analysis and power the study to get precise estimates (relative standard error $\leq 20\%$) of the mean clearance parameter in renal and hepatic impaired

patients. For further information, see hepatic and renal impairment guidances. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>).

2. Inclusion criteria for the planned phase 3 trial (PR-30-5011-C) indicate that patients with CrCl < 60 mL/min, and patients with moderate or severe hepatic impairment (NCI Criteria) will not be enrolled. It is not clear whether you have PK data from patients in these sub populations from other trials. Please propose how you intend to address dosing recommendations in these patients.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
 - if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
 - if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KIM J ROBERTSON
03/20/2015



IND 100996

ADVICE/INFORMATION REQUEST

TESARO, Inc.
Attention: Kathleen Andrade
Senior Manager Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Andrade:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for niraparib (MK-4827).

We also refer to your amendment dated December 23, 2014, containing your plan for pharmacology/toxicology development.

We have the following comments and recommendations:

We do not agree that completed and planned nonclinical studies presented in the tabulated summary of studies submitted to your IND on December 23, 2014, are adequate to support approval of niraparib. Conduct genetic toxicology studies performed according to recommendations in ICH S2 that are compliant with GLP regulations (21 CFR part 58) to support an NDA submission for niraparib. If we determine that niraparib is genotoxic, based on our review of the results from an adequate battery of GLP genetic toxicology studies, then we agree that embryo-fetal developmental toxicity studies with niraparib are not needed to support an NDA for the proposed indication, as recommended in ICH S9 based on the toxicity of niraparib. The acceptability of nonclinical data to support approval of an NDA for niraparib will be determined following our review of your NDA submission.

Additionally, submit final reports from the 3-month repeat-dose toxicology studies in rats and dogs with niraparib to your IND to support conducting a phase 3 clinical trial, as recommended in ICH S9.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GEOFFREY S KIM
03/25/2015



IND 100996

MEETING MINUTES

TESARO Inc.
Attention: Thomas F. Perrone, Ph.D., RAC
Director, CMC Regulatory Affairs
1000 Winter St., #3300
Waltham, MA 02451

Dear Dr. Perrone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Niraparib (MK-4827).

We also refer to the telecon between representatives of your firm and the FDA on February 17, 2015. The purpose of the meeting was to CMC-related advice on the approach for controlling drug substance and drug product manufacturing as well as the stability approach to supporting a future NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathy Tran-Zwanetz, Acting Branch Chief at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief, Branch II
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date and Time: February 17, 2015, 2:00 PM – 3:00 PM
Application Number: IND 100996
Product Name: Niraparib
Indication: Ovarian cancer
Sponsor/Applicant Name: Tesaro Inc.
Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Cathy Tran-Zwanetz

FDA ATTENDEES

Kasturi Srinivasachar, Ph.D., Office of New Drug Product Reviewer
Katherine Windsor, Ph.D., Office of New Drug Product Reviewer
Olen Stephens, Ph.D., Office of New Drug Acting Branch Chief
Cathy Tran-Zwanetz, Office of Process and Regulatory Process Acting Branch Chief

SPONSOR ATTENDEES

Mary Lynne Hedley, Ph.D., President and Chief Scientific Officer
Thomas F. Perrone, Ph.D., Director, CMC Regulatory Affairs
Nanor Karagozian, M.Sc., Sr. Manager, CMC Regulatory Affairs
Tanya Lewis, Vice President, Regulatory Affairs
Stephen Ruddy, PhD, Vice President, Pharmaceutical Development
George Wu, Ph.D., Vice President, Pharmaceutical Sciences

1.0 BACKGROUND

The purpose of this meeting is to discuss CMC-related advice on the approach for controlling drug substance and drug product manufacturing as well as the stability approach to supporting a future NDA. FDA sent preliminary comments on February 2, 2015.

2. DISCUSSION

1. Does the Agency concur with our proposed designation of the (b) (4) as the regulatory starting material?

FDA Response:

No, the Agency does not agree with your proposed starting material designation. Your proposed drug substance starting material, (b) (4)

We remind you that final assessment of starting materials, including impurity qualification, will be re-evaluated or performed during NDA review.

Discussion:

TESARO agreed to push back the regulatory starting material designation to (b) (4) as described in the meeting package. TESARO sought further clarification on the thinking behind FDA's starting material designation, (b) (4)

TESARO confirmed that they are (b) (4) TESARO reaffirmed that they will redesignate the regulatory starting materials as (b) (4)

2. Does the Agency concur with TESARO's proposed specifications for (b) (4)?

FDA Response:

Refer to the Agency's Response to Q1. Your proposed specification for the (b) (4) appear to be reasonable. However, the adequacy of your specifications for your starting materials will be a review issue.

Discussion:

See discussion point 1.

3. Niraparib is a genotoxic compound and is administered to patients with advanced cancer at a daily dose of up to 300 mg. In keeping with *Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*, TESARO plans to apply both the identification (0.10%) and the qualification thresholds (0.15%) stated in ICH Q3A and Q3B to niraparib impurities including potential genotoxic impurities (PGIs). Does the Agency agree with our strategy?

FDA Response:

We agree with your strategy to control potential genotoxic impurities for this patient population is consistent with ICH S9 and is acceptable. Please note that our concurrence is specific to this particular case with this specific patient population.

Discussion:

No further discussion.

4. TESARO plans to have at least 9 months of stability data for the primary stability batches of DS and up to 24 months of supportive stability data at the time of the NDA submission (ovarian cancer indication). Does the Agency agree that 9 months of primary stability data for DS are adequate to support submission of the NDA?

FDA Response:

We expect 12 months of stability data for each of three registration batches at the time of the NDA submission, per ICH Q1A. 9 months of data can be submitted in your original NDA and an additional 3 months – 12 total – within 30 days of submission.

Discussion:

No further discussion.

5. TESARO plans to submit at least 9 months of long-term primary and 6 months of accelerated stability data for the DS manufactured by the intended commercial route in the initial NDA. Should the Agency indicate that 9 months DS primary stability are not adequate to support the submission of the NDA, would the Agency agree to accept additional stability data during the review of the NDA?

FDA Response:

Refer to the Agency's Response to Q4.

Discussion:

No further discussion.

6. TESARO plans to have at least 6 months of stability data for the primary stability batches of Drug Product (DP) and up to 24 months of supportive stability data at the time of the NDA submission (ovarian cancer indication). Does the Agency agree that 6 months of primary stability data for DP are adequate to support submission of the NDA?

FDA Response:

Refer to the Agency's Response to Q4.

Discussion:

No further discussion.

7. TESARO plans to request a shelf life in the initial NDA submission of 12 months for DP based on at least 6 months of long-term and 6 months of accelerated primary stability data for the DP manufactured by the intended commercial route. Should the Agency indicate that 6 months of DP primary stability are not adequate to support the submission of the NDA, would the Agency agree to accept additional stability data during the review of the NDA?

FDA Response:

Refer to our response to Q6. Shelf life will be determined based on the data submitted to the NDA. Our expectation is that any stability update would be submitted within 30 days of NDA submission.

Discussion:

No further discussion.

Additional FDA Comment:

We recommend that you reach out to the Division of Biopharmaceutics to discuss your dissolution method and acceptance criteria through the Office of Program and Regulatory Operations (OPRO) Regulatory Business Process Manager, Rabiya Laiq.

APPEARS THIS WAY ON ORIGINAL

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

/s/

OLEN M STEPHENS
03/02/2015



NDA 208447

INFORMATION REQUEST

Tesaro, Inc.
Attention: Charles A. Miller
Vice President Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated and received October 31, 2016, submitted under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act for niraparib capsule, 100mg.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Process:

1. We note that your proposed in-process controls for the commercial manufacturing are different than those used in the registration batches. Include all the IPCs used during registration batches [REDACTED] (b) (4) to your commercial batches.

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834. Please respond to drug process comments by COB February 24, 2017.

Sincerely,
**Kristine F.
Leahy -S**

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2017.02.23 10:55:53 -05'00'



IND 100996

MEETING MINUTES

TESARO, Inc.
Attention: Tanya Lewis
Regulatory Affairs
1000 Winter Street
Suite 3300
Waltham, MA 02451

Dear Ms. Lewis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Niraparib (MK-4827).

We also refer to the meeting between representatives of your firm and the FDA on February 13, 2013. The purpose of the meeting was to discuss TESARO's continued clinical development plans in ovarian (b) (4).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kim J. Robertson, Regulatory Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: February 13, 2013; 1:00pm-2:00pm
Meeting Location: Bldg. #22, Conf. Room 1415

Application Number: 100996
Product Name: Niraparib (MK-4827)
Indication: Treatment of (b) (4) ovarian cancer)
Sponsor/Applicant Name: TESARO, Inc.

Meeting Chair: Amy McKee, M.D.
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Robert L. Justice, M.D., M.S., DOP1/OHOP
Amna Ibrahim, M.D, DOP1/OHOP
Amy McKee, M.D., Clinical Team Leader, DOP1/OHOP
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV/OB
Stella Karuri, Ph.D., Biometrics Reviewer, DBV/OB
Todd Palmby, Ph.D., Non-Clinical Team Leader, DHOT/OHOP
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCPV/OCP
Elimika Pfuma, Ph.D., Clinical Pharmacology Reviewer, DCPV/OCP
LT Jessica Voqui, PharmD, M.S., SEALD Reviewer, OMPT/OND
Sharon (Xueying) Liang, M.D., Ph.D., Scientific Reviewer, DIHD/OIR
Abraham Tzou, M.D., Clinical Reviewer, DHID/OIR
Reena Philip, Ph.D., Deputy Division Director, DIHD/OIR

SPONSOR ATTENDEES

David G. Brooks, M.D., Ph.D., Head, Translational Medicine, TESARO
Mary Lynne Hedley, Ph.D., President & Chief Scientific Officer, TESARO
Tanya Lewis, Vice President, Regulatory Affairs, TESARO
Robert Martell, M.D., Ph.D., Chief Medical Officer to TESARO
Sujata Arora, Biostatistics Consultant to TESARO
Stacie Hudgens PRO Consultant to TESARO

DOP 1
Meeting Minutes
Type B, EOP 2

SPONSOR ATTENDEES (cont.)

[REDACTED] (b) (4)

Medical Gynecologic Oncology, Dana Farber Cancer Institute; Associate Professor of
Medicine, Harvard Medical School

APPEARS THIS WAY ON ORIGINAL

1.0 BACKGROUND

TESARO, Inc. has requested a Type B meeting to discuss clinical development plans for niraparib (MK-4827) in ovarian cancer. An initial Phase 1a/b clinical investigation of niraparib (Protocol MK-4827-001) in advanced solid tumors with cohort expansion to ovarian cancer was initiated in 2008 by Merck. Based on the results from this study, TESARO is proposing a Phase III double-blind, randomized, placebo controlled study for maintenance therapy in relapsed, platinum sensitive ovarian cancer patients who have either gBRCAmut or a tumor with high grade serous histology.

Niraparib is an orally active PARP 1/2 inhibitor. Preclinical models have observed niraparib to induce synthetic lethality when administered to cells with homologous recombination defects (i.e. BRCA1 or BRCA2 mutation). In a BRCA1 mutant xenograft study, niraparib dosed orally caused tumor regression by >90% reduction in tumor weight compared to control; in a BRCA2 mutant xenograft study, niraparib dosed mice showed 55-60% growth inhibition, both by tumor volume and weight.

The IND for niraparib (MK-4827) has been active since 2008

(b) (4)

An initial Phase 1a/b clinical investigation of niraparib (Protocol MK-4827-001) in advanced solid tumors with cohort expansion to ovarian cancer was initiated in 2008 by Merck. This study was completed by Merck and a dose of 300 mg QD was identified as the recommended Phase 2 dose (RP2D). A total of 104 patients were treated in this study, including 49 ovarian and 12 breast cancer patients. Objective responses were observed in patients with breast and ovarian cancer, in patients who were platinum-sensitive or platinum resistant, and in patients with and without germline BRCA mutation. Response rates were higher in patients defined as germline BRCA mutation carriers.

RECIST partial responses (PR) in the ovarian population evaluable for response (n=43):

Regardless of BRCA status:

Platinum sensitive: 7 of 13 (54%)

Platinum resistant: 6 of 29 (21%)

BRCA mutation status:

Present: 9 of 20 (45%)

Platinum sensitive: 6 of 10 (60%)

Platinum resistant: 3 of 9 (33%)

Absent: 5 of 23 (22%)

Meeting Minutes
Type B, EOP 2

The most common adverse events potentially related to niraparib are fatigue, nausea, neutropenia, anemia, thrombocytopenia, anorexia, vomiting and constipation.

2. DISCUSSION

2.1. Category/Discipline

List of questions for discussion

The list of questions (grouped by discipline) for discussion at this meeting is presented below:

3.1.1. Chemistry, Manufacturing and Controls

There are no questions relating to chemistry, manufacturing, and controls (CMC) at this time. A separate meeting will be requested to discuss the CMC plans and activities proposed to support registration of niraparib.

3.1.2. Non-clinical

There are no questions relating to non-clinical development at this time. A non-clinical data package and strategy will be submitted to FDA for advice regarding its sufficiency to support registration in the proposed indications. [Appendix 11.4](#) contains summary tables for the non-clinical studies conducted to date for niraparib.

3.1.3. Clinical

General

1. The Sponsor plans to conduct the proposed clinical studies using a niraparib dose of 300 mg provided as continuous daily dosing. This dose and schedule was defined as the maximum tolerated dose and was considered a well-tolerated dose that provided clinical activity in the Phase 1 dose escalation study. Does the FDA agree that this is the appropriate dose and schedule to use for conduct of the Phase 3 registration studies in ovarian (b) (4) cancer?

FDA Response: This appears to be an appropriate dose and schedule for the Phase 3 trial.

Meeting Discussion: No further discussion was necessary.

The Sponsor plans to utilize an enrichment approach in both studies to identify patients based on germline BRCA mutation status. Germline BRCA tests are performed by sequencing of PCR amplified DNA sequences and interrogation of recurrent rearrangements throughout the world. Internationally recognized standards of Molecular Pathology and Clinical Genetics are used to annotate which mutations are deleterious in large, commonly referenced databases ([Chenevix, 2006](#)). Thus, a significant degree of inter-country concordance is observed for analysis and interpretation of test results and hence gBRCA status. BRCA

mutation testing will be performed prior to randomization using locally available standard tests and patients will be assigned to cohorts based on these results. A separate randomization list will be created for each cohort. The primary endpoint will be analyzed based on these results. All patients enrolled at US sites will be identified as gBRCA^{mut} by BRACAnalysis®, a LDT (Laboratory Developed Test) developed and commercialized by Myriad Genetics Laboratories, Inc. BRACAnalysis® is the only commercially available BRCA test in the US due to patent exclusivity and has become the US standard for the identification of individuals with hereditary (b) (4) ovarian cancer during 16 years of use in over 1 million samples analyzed. However, BRACAnalysis® is not widely used outside of the US. Patients enrolled at non-US sites will also have blood tested by the BRACAnalysis® test to assess sensitivity and specificity of the tests performed ex-US in comparison to the US standard.

2. Does FDA agree with this method of assessing germline BRCA mutation status as an enrichment strategy for defining the patient population and as a mechanism to assign patients to cohorts for determination of the primary endpoint analysis in the proposed ovarian (b) (4) clinical studies with niraparib?

FDA Response: We do not recommend that you use the proposed testing method for enrichment in this clinical trial, because your enrollment criteria would be based on a number of different tests, with possibly different interpretation algorithms. We do not object to use of a BRCA test as a mechanism to assign patients to cohorts.

We recommend you to use a single, analytically validated test to determine BRCA mutation status for enrollment on all patients. This will allow a valid analysis of test/therapy interaction, and will provide a single set of analytical performance parameters to which any new test (if contemplated) could be bridged. Alternatively, we recommend that you use the test that will be marketed in the clinical trials(s).

It is possible that your trial could lead to a drug claim that would require a companion diagnostic test for BRCA mutations. We recommend that you consider this possibility and plan appropriately for it. We encourage you to discuss any plans for a companion diagnostic test with CDRH/OIR through our Pre-Submission process.

For your reference, please refer to the following draft guidance documents on In Vitro Companion Diagnostic Devices and the Pre-Submission Program.

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

Meeting Discussion: The sponsor plans to test all patients for BRCA mutations using centralized testing on enrollment. If this trial shows a clinical benefit only for patients with germline BRCA mutations, the sponsor will bridge the centralized testing to a

companion in vitro diagnostic, which should be approved contemporaneously with an NDA. The Agency recommends that a meeting request be sent to CDRH.

3. To verify platinum sensitivity for the penultimate (next to last) platinum regimen, TESARO will evaluate and record source documentation (ie scan reports, clinic notes, laboratory evaluations) to ensure disease progression occurred ≥ 6 months after completion of each patient's penultimate platinum based chemotherapy regimen. For entry onto study, only patients with apparent benefit from the last course of platinum therapy will be entered (patients with no measurable disease >2 cm (per Investigator assessment) and normal CA125. Does the Agency agree with the method of assessing platinum sensitivity and the disease status at study entry?

FDA Response: Patients should have a confirmed objective response (PR or CR) and disease progression after ≥ 6 months per source documents for the penultimate platinum therapy. However, we recommend that you stratify based upon response to the ultimate platinum therapy.

Please justify why you will be including patients who do not have a PR or CR (i.e. stable disease) to the ultimate platinum therapy.

Meeting Discussion: The Agency cautioned that not stratifying based upon response is at the sponsor's own risk. The sponsor intends to document response for the prior platinum regimens based upon source documentation, such as radiology reports and other clinical records. The Agency clarified that the trial may enroll based upon the benefit from last platinum therapy defined as no measurable disease >2 cm (per Investigator assessment) and normal CA125.

4. The proposed study has a placebo comparator because clinical practice standards for this population allow discontinuation of treatment with platinum based chemotherapy if a response is achieved, due to intolerable toxicities that occur with cumulative treatment and lack of additional benefit from further treatment. Patients are then followed, with no further treatment, until disease progression. Does FDA agree with the choice of placebo as an appropriate comparator in patients with platinum sensitive relapsed ovarian cancer who have no measurable disease >2 cm and normal CA125 following their most recent platinum-based regimen?

FDA Response: Yes.

Meeting Discussion: No further discussion was necessary.

5. There is a clinically well-established observation that the intra-patient chemotherapy free interval decreases incrementally with each subsequent round of platinum based chemotherapy in patients with platinum sensitive ovarian cancer, and this effect has been described on a population basis ([Hanker, 2012](#); [Markman, 2004](#)). Moreover, the current standard approach is to follow a patient for progression, in the absence of active treatment, if a response is achieved to a platinum containing regimen. Improvement in PFS reflects a

lengthening of the period of time during which patients are without clinical disease-related symptoms and the need for additional IV based cytotoxic and poorly tolerated chemotherapy, the current standard of care in this patient population, is delayed. In this small well-defined and enriched population improvement in progression-free survival (PFS) (for example, 4.8 to 9.6 months, Hazard ratio [HR] =0.5) would represent a meaningful benefit to patients. In this study, TESARO proposes that the primary endpoint analysis will be on PFS and each cohort is sufficiently powered to detect a prolongation of PFS from 4.8 to 9.6 months (HR=0.5). The analyses of the PFS endpoints in the two cohorts are independent and address separate hypotheses concerning the germline BRCA enriched and non germline BRCA populations. Therefore, within each cohort, the overall family-wise error rate will be controlled at 1-sided alpha=0.025 and the primary endpoint of PFS will be tested at 1-sided alpha 0.025 for each cohort. Does the FDA agree that the proposed statistical approach for analysis of PFS in each of the defined patient populations is acceptable and that the PFS data will be acceptable to support approval in each of the analyzed populations if a robust and clinically meaningful PFS benefit, such as that described, and an acceptable safety/tolerability profile, supported by no detriment in overall survival, is demonstrated?

FDA Response: No. The clinical benefit of PFS improvement in the maintenance setting has not been established. A statistically significant difference in PFS may not demonstrate a clinically meaningful difference. We recommend using OS as a primary or co-primary endpoint.

Meeting Discussion: The Agency reiterated its position but clarified that the statistical approach for analyzing PFS is acceptable.

6. To support the PFS data, TESARO plans to evaluate the effect of niraparib on patient symptoms and function via the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI). Similarly, the European Quality of Life scale, 5 Dimensions (EQ-5D) will be included to evaluate general health related quality of life. The PRO evaluations will be administered at baseline and every 2 months for the first year, then every 3 months until 2 years post randomization. These evaluations will continue even if a patient has progressive disease in order to capture post study drug treatment disease symptoms and morbidity from subsequent chemotherapy. PRO is a key secondary endpoint and will be tested in a hierarchical manner for statistical significance within a given cohort if the PFS endpoint for the cohort is statistically significant. If the FOSI analysis achieves statistical significance (one-sided significance level of 0.025), the EQ-5D Index Score, which measures general health related quality of life, will then be tested in the same manner. A multivariate longitudinal mixed-effects growth curve model with a first-order auto-regressive covariance pattern to account for the relationship between adjacent assessments, will be conducted on score changes at each assessment for the FOSI total score. Fixed effects and interaction terms will be evaluated in each model using maximum-likelihood estimation and will include treatment arm, time to progression after the penultimate platinum therapy before study enrollment, prior use of bevacizumab in conjunction with the penultimate or last platinum regimen, and number of prior platinum regimens. An individual patient's rate of change will

be included in each model as a random factor to account for between-patient variability. Does the FDA agree that the FOSI and EQ-5D are appropriate instruments to assess the effect of niraparib and post study treatments on patient symptoms and general health related quality of life, that the timing of the evaluations are suitable and that the proposed analyses are appropriate for the intended use to support clinical benefit associated with the PFS endpoint?

FDA Response: No, we do not agree that these instruments are appropriate to support labeling claims. In our experience, the FACT (FOSI) and EQ-5D have not been demonstrated to be adequate to establish claims of treatment benefit.

We have the following concerns regarding these assessments:

- **The FOSI includes items that evaluate a range of symptoms, adverse events, and health-related impacts of disease (e.g., worry, feeling content). As stated in the FDA *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (PRO Guidance)*, combining distinct symptoms, adverse events, and impacts into a single summary score, without first evaluating each concept independently is not recommended. We do not recommend combining treatment harms and benefits into a single overall measure because this does not allow for the evaluation of the investigational treatment's risks separately from its benefits.**
- **Concerning the FOSI questionnaire, the 7-day recall period may not be appropriate for all the concepts being measured (e.g., pain).**
- **The EQ-5D is a measure of quality-adjusted-life-years intended to provide a single index value for use in economic analysis. As a disease-generic measure used in economic evaluation, the EQ-5D does not have content validity for use in estimating treatment benefit for labeling claims. These assessments are commonly requested by European regulatory authorities and payors.**

A PRO instrument intended to support labeling claims of treatment benefit should be submitted with supportive documentation for Agency review to ensure it is a valid and reliable assessment according to the principles specified in the FDA *PRO Guidance*. Once the content validity has been established for the PRO instrument, then we can assess whether the timing of the assessments and proposed analyses are appropriate.

Meeting Discussion: The sponsor will perform descriptive analyses of PRO measurements as a secondary endpoint. Although stated in the original question in the meeting briefing package, there will be no hierarchical testing for this exploratory endpoint, nor will PRO measurements be used for labeling claims. The Agency noted that analysis of PRO data after a patient is no longer receiving niraparib and/or is receiving subsequent therapy will be difficult to interpret for regulatory purposes.

7. Formal assessment of PFS will be performed using RECIST 1.1 criteria from centrally-reviewed imaging. Tumor imaging will occur every 8 weeks for the first year and every 12 weeks thereafter. CA125 may be used to prompt unscheduled imaging, but CA125 will not be considered as a determinant of progression. Does the FDA agree with this approach to measuring PFS in the ovarian cancer setting?

FDA Response: Yes. However, ovarian cancer can be very difficult to assess radiographically, and you will need to demonstrate a large difference in PFS between arms, or use OS as a primary endpoint. See response to question #8.

Meeting Discussion: No further discussion was necessary.

8. Evidence supporting the approval of niraparib in the maintenance of a response to a platinum containing chemotherapy regimen in platinum-sensitive relapsed ovarian cancer patients enriched for gBRCA^{mut} as well as in the non gBRCA^{mut} population would come from results of the Phase 3 study described above targeting a meaningful prolongation of PFS with supportive PRO data, an acceptable safety/tolerability profile and no detriment in survival. This data will be supported by data from a Phase 1 study in 104 patients including 49 patients with ovarian cancer. Would FDA consider regular approval of niraparib for the maintenance of a response to a platinum containing chemotherapy regimen in patients with platinum-sensitive relapsed ovarian cancer patients based upon the totality of the evidence from the two studies described above?

FDA Response: The clinical benefit of PFS improvement in the maintenance setting has not been established. At this time, you have limited data from a small number of patients. Niraparib may perform differently than other PARP inhibitors reported in the literature you have cited. You may want to consider conducting a Phase 2 trial to confirm your findings prior to proceeding to a larger Phase 3 trial. Whether this trial will support approval will be a review issue that is dependent on the benefit-risk profile of niraparib. A statistically significant difference in PFS may not demonstrate a clinically meaningful difference. We recommend using OS as a primary or co-primary endpoint.

For a single randomized trial to support an NDA, the trial must be well-designed, flawlessly executed, and internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

Meeting Discussion: No further discussion was necessary.

- 9.

(b) (4)

[Redacted] (b) (4)

FDA Response: This question will need to be submitted with your meeting request [Redacted] (b) (4)

Meeting Discussion: No further discussion was necessary.

10.

[Redacted] (b) (4)

FDA Response: This question will need to be submitted with your meeting request [Redacted] (b) (4)

Meeting Discussion: No further discussion was necessary.

11.

[Redacted] (b) (4)

FDA Response: This question will need to be submitted with your meeting request [Redacted] (b) (4)

Meeting Discussion: No further discussion was necessary.

Additional Comments:

In the Investigator’s Brochure for niraparib you report twelve out of the 104 patients on Study PN001 to have had a prolonged QTc. Seven of these twelve patients received a dose of niraparib at 300mg QD. Have there been any safety reports of Torsades de pointes, sudden death or other cardiac sequelae in any of the patients with prolonged QTc from any of the studies? A more rigorous evaluation of QTc prolongation will need to be conducted prior to submission of an NDA.

In general, a ‘thorough QT’ study should be conducted. In oncology, alternative proposals to the ‘thorough QT’ study including ECG collection with time matched PK sampling may be appropriate. Submit a QT evaluation plan for QT-IRT review. Until this dedicated clinical trial is conducted to rule out the QT prolongation potential of the study drug, include ECG monitoring at baseline, around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment in all clinical trials. Refer to the Guidance for Industry entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>.

TESARO Inc.’s Response to FDA (February 13, 2013): In prior niraparib studies there have been no Torsades de pointes, sudden death or other significant cardiac sequelae in the patients with prolonged QTc. ECG monitoring at baseline around the anticipated maximal and steady-state plasma concentrations, as clinically indicated, and at the end of treatment will be incorporated into the planned phase 3 study. We will incorporate thorough ECG collection with time matched PK sampling in a subset of patients as part of the planned phase 3 study. The protocol for the planned phase 3 study will be submitted to FDA for review and comment.

Meeting Discussion: The Agency requested that the sponsor submits a QT evaluation plan for QT-IRT review.

Regarding the Proposed Phase 3 trials

- **Please clarify and provide the justification for how you intend to dose niraparib in regards to food in the proposed phase 3 trials.**

TESARO Inc.’s Response to FDA (February 13, 2013): Patients were not fasted in the previous phase 1 study, therefore we currently do not include guidance around administration of niraparib in the fasted or fed state. We will incorporate an evaluation of fasted/fed state in a subset of patients in the planned phase 3 study which will be submitted for review and comment by the Agency.

Meeting Minutes
Type B, EOP 2

Meeting Discussion: The Agency strongly recommends that the sponsor evaluates food effect prior to the start of their Phase 3 trial. The sponsor stated that they would propose a plan to the Agency at a later date.

During Drug development

- We recommend that you request a Type C meeting to discuss your clinical pharmacology development plan.

TESARO Inc.'s Response to FDA (February 13, 2013): The sponsor will request a Type C meeting to discuss the clinical pharmacology development plan for niraparib.

Meeting Discussion: No further discussion was necessary.

- Identify the pathways by which niraparib and its active metabolite(s) are eliminated to determine the need to conduct dedicated organ impairment trial(s). Refer to the Guidances for Industry entitled “*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> and “*Pharmacokinetics in Patients with Impaired Hepatic Function : Study Design, Data Analysis, and Impact on Dosing and Labeling*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

TESARO Inc.'s Response to FDA (February 13, 2013): The sponsor will determine the need to conduct dedicated organ impairment trials and submit a plan for Agency review and comment.

Meeting Discussion: Due to lack of time, no further discussion took place.

- Evaluate food effect on the bioavailability of niraparib. Food-effect bioavailability information should be available to guide dosing recommendations with regard to food intake for the clinical efficacy and safety trials. Conduct a food effect trial per Guidance for Industry entitled “*Food-Effect Bioavailability and Fed Bioequivalence Studies*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf>

TESARO Inc.'s Response to FDA (February 13, 2013): We will incorporate an evaluation of fasted/fed state in a subset of patients in the planned phase 3 study, which will be submitted for review and comment by the Agency

Meeting Discussion: Due to lack of time, no discussion took place.

Nonclinical Drug development

- **Based on information in your briefing package, you do not appear to have conducted 3-month repeat dose nonclinical toxicology studies to support your proposed Phase 3 clinical trial, which is not consistent with recommendations in ICH S9**
[\[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf\]](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.pdf). If you proceed with conducting a Phase 3 clinical trial, conduct 3-month repeat-dose toxicology studies and submit the results to your IND. If you plan to initiate a Phase 3 trial prior to submitting data from the 3-month toxicology studies, provide a timeline of when the results from these studies will be submitted and a justification for your proposal

TESARO Inc.'s Response to FDA (February 13, 2013): The Sponsor initiated 3 month GLP toxicology studies in February 2013. The sponsor plans to initiate the proposed clinical study in June 2013 which is after any clinical observations from the 3 month toxicology study would be available (May 2013). Clinical pathology from the 3 month toxicology studies are expected to be available in June 2013. Histopathology results and draft reports are expected to be available in August with audited draft reports available in September and final reports in October. We intend to submit the reports to the IND at that time. The sponsor believes that this is an acceptable approach based upon clinical data obtained to date in 144 patients. Clinical exposure in responding patients has been significant, for example the median duration of treatment for responding patients with platinum sensitive ovarian cancer was 429 days. Collectively these data provide evidence of the long term safety profile of niraparib.

Meeting Discussion: Due to lack of time, no discussion took place.

3.0

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

Meeting Minutes
Type B, EOP 2

TESARO Inc.’s Response to FDA (February 13, 2013): The sponsor plans to request a waiver from the requirement to evaluate niraparib in pediatric patients as ovarian cancer does not occur in pediatric patients. The waiver will be requested within 60 days of the scheduled end of phase 2 meeting.

Meeting Discussion: Due to lack of time, no discussion took place.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Meeting Minutes
Type B, EOP 2

Action Item/Description	Owner	Due Date
The Agency will send TESARO, Inc. the template for QT-IRT evaluation plan.	FDA	Sent as a separate attachment with official meeting minutes.
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

6.0 ATTACHMENTS AND HANDOUTS

N/A

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/s/

AMY E MCKEE
02/22/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208447

LATE-CYCLE MEETING MINUTES

TESARO, Inc.
Attention: Charles A. Miller
Vice President, Regulatory Affairs
1000 Winter St., Suite 3300
Waltham, MA 02541

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated October 31, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zejula™ (niraparib) Capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 7, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: March 7, 2017; 1:00-2:00 pm
Meeting Location: T-con

Application Number: NDA 208447
Product Name: Zejula™ (niraparib)
Applicant Name: TESARO, Inc.

Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
Laleh Amiri-Kordestani, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Lynn Howie, MD, Clinical Reviewer, DOP1
William Pierce, PharmD, Associate Director for Labeling
Michael Brave, MD, Clinical Reviewer, DOP1
Pengfei Song, PhD, Clinical Pharmacology Team leader, DCP V
Vadryn Pierre, PhD, Clinical Pharmacology Reviewer, DCP V
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Lijun Zhang, PhD, Biometrics Reviewer, DBV
Todd Palmby, PhD, Pharmacology Toxicology Supervisor, DHOT
Wimolnut Manheng, PhD, Pharmacology Toxicology Reviewer, DHOT
Xiao-Hong Chen, PhD, Pharmaceutical Assessment Lead, ONDP
William Adams, PhD, Quality Reviewer, ONDP
Hisani Madison, PhD, MPH, Regulatory Scientist, CDRH/OIR/DMGP
Morgan Walker, PharmD, MBA, CPH, Patient Labeling Reviewer, DMPP
Jeannette Dinin, Regulatory Project Manager, DOP1

APPLICANT ATTENDEES

Shefali Agarwal, MD, MPH, Senior Medical Director, Clinical Science
Mary Lynne Hedley, PhD, President, Chief Operating Officer
Martin Huber, MD, SVP, Chief Medical Officer
Jennifer Jackson, PhD, SVP, Global Regulatory Affairs and Quality Assurance
Dave Lust, MS, Exec. Director, Regulatory CMC
Colleen McGraw, Director, Regulatory Affairs, Labeling
Chuck Miller, VP, Regulatory Affairs

Seth Miller, Director, Regulatory Affairs, Strategy
Ilker Yalcin, PhD, VP, Biostatistics

1.0 BACKGROUND

NDA 208447 was submitted on October 31, 2016, for Zejula™ (niraparib)

Proposed indication(s): Maintenance or treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following a complete or partial response to platinum-based chemotherapy.

PDUFA goal date: June 30, 2017

FDA issued a Background Package in preparation for this meeting on March 2, 2017.

2.0 DISCUSSION

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

There are no substantive review issues at this time.

Advisory Committee Meeting

An Advisory Committee meeting is not planned.

REMS or Other Management Actions

No issues related to risk management have been identified to date.

LCM Agenda

1. Discussion of Substantive Review Issues
 - **Cardiovascular events**
2. Major labeling issues – **The Division stated that it is important to submit all changes in tracked changes form when working on the label. The Division lost time once we realized that not all changes had been tracked and we had been working on a label that needed to be replaced with a tracked changes version.**

The Division will be sending you additional revisions to the label with accompanying rationale shortly. Some changes were rejected and some of changes were retained.

3. Postmarketing Requirements/Postmarketing Commitments – **All PMCs and PMRs have agreed content and timelines.**
4. Review Plans – **The Division is working towards an expedited review.**

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

LALEH AMIRI KORDESTANI
03/24/2017