CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208558Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208558 SUPPL # HFD # 150

Trade Name Lynparza®

Generic Name Olaparib

Applicant Name AstraZeneca

Approval Date, If Known August 17, 2017

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) Type 3 NDA

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?

Reference ID: 4140542

3 years

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# 206162 Olaparib Capsules

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

Reference ID: 4140542

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:

Study 19, "Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens."

SOLO2, “Phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.”

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 Study 19	YES ☐	NO ☒
Investigation #2 SOLO-2	YES ☐	NO ☒
Investigation #3	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 Study 19	YES ☐	NO ☒
Investigation #2 SOLO-2	YES ☐	NO ☒
Investigation #3	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"):

Study 19, "Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens."

SOLO2, "Phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy."

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 Study 19		!
IND # 075918	YES ☒	! NO ☐ ! Explain:

Investigation #2 SOLO-2		!
IND # 75918	YES ☒	! NO ☐ ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Rajesh Venugopal
Title: Senior Regulatory Project Manager
Date: July 5, 2017

Name of Office/Division Director signing form: Julia Beaver, MD
Title: Acting Division Director/OHOP/DOP1

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

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

/s/

RAJESH VENUGOPAL
08/17/2017

JULIA A BEAVER
08/17/2017

Reference ID: 4144926

PEDIATRIC PAGE REPORT

March 6, 2017 10:46:50 AM GMT-05:00

Selection Criteria:

Appl Type Number:	**NDA 208558**
Submission Type(s):	**ORIG**
Sort Order:	**Appl Type No**

<Reports start from Page 2>

DARRTS 702A

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Appears this way on original

Reference ID: 4144926

Best Available Copy

Organization: DOP1 Product Name: LYNPARZA™ (OLAPARIB)
Appl Type No: NDA 208558 Applicant: ASTRAZENECA PHARMACEUTICALS LP
Submission Type #: ORIG - 1 Submission Status: PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
2/22/2017	TABLET	N	2/22/2017	8/22/2017	TYPE 3	OVARIAN CANCER.

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
3.167	WAIVED	FULL	0	16	DISEASE/CONDITION DOES NOT EXIST IN CHILDREN		

Reference ID: 4144926

Orga	Product	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosag	Orph	Subm	Goal Du	Submi	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DO	LYNPR	NDA	ORIG -	AST	PEN	2/22/20	TABL	N	2/22/	8/22/2	TYP	O	3	WAIV	FUL	0	16	DIS		

1.3.3 DEBARMENT CERTIFICATION

Re: **NDA 208,558**

Lynparza™ (olaparib) tablets

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Howard G. Hutchinson,
US Regional VP, Regulatory Affairs & Policy
AstraZeneca Pharmaceuticals LP

Reference ID: 4144926

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208558	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: LYNPARZA™ Established/Proper Name: Olaparib Dosage Form: Tablets, 100 mg, 150 mg		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable): N/A
RPM: Rajesh Venugopal		Division: Division of Oncology Products 1

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action - August 17, 2017 • User Fee Goal Date is August 22, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 N/A	☐ 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.

Reference ID: 4141537

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 3
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other 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	☒ No ☐ 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.	☒ Verified ☐ 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)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approval - 8/17/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 8/9/17
• Original applicant-proposed labeling	☒ Included 2/22/17
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 8/9/17
• Original applicant-proposed labeling	☒ Included Submitted 2/22/17
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 7/21/17
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Conditionally Acceptable: 5/26/17 DMEPA Review Date: 5/23/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 8/16/17 DMEPA: ☒ 7/10/17; 6/21/17; 5/23/17 DMPP/PLT (DRISK): ☒ 7/11/17 OPDP: ☒ 7/11/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing review – 3/24/17 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

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

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC July 19, 2017 If PeRC review not necessary, explain: _____	Full Waiver
❖ Breakthrough Therapy Designation	☐
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Denied 5/15/13
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	8/14/17; 8/0/17; 8/9/17 (2); 8/7/17(2); 7/28/17; 7/26/17; 7/24/17(2); 7/19/17; 7/14/17(3); 7/12/17; 7/10/17; 6/28/17; 6/27/17 (2); 6/26/17; 5/26/17; 5/19/17; 5/18/17; 5/17/17; 5/12/17; 5/11/17; 5/8/17; 5/5/17; 5/4/17; 5/2/17; 4/28/17; 4/13/17(2); 4/7/17; 4/4/17; 3/29/17(2); 3/28/17; 3/24/17 (2); 3/23/17(2); 3/22/17; 3/21/17(2); 3/20/17; 3/17/17; 3/14/17; 3/13/17; 3/9/17; 2/23/17; 2/3/17; 1/23/17
❖ 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)	T-Cons: 8/8/17; 7/6/17; 6/13/17; 5/30/17; 5/23/17
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/12/17
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ Informal t-con 5/18/17
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 8/14/17; See multidisciplinary review dated 8/15/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/14/17; See multidisciplinary review dated 8/15/17
PMR/PMC Development Templates *(indicate total number)*	☐ None Included; 3 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review See multidisciplinary review dated 8/15/17
• Clinical review(s) *(indicate date for each review)*	☒ No separate review 8/11/17; See multidisciplinary review dated 8/15/17
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See multidisciplinary review dated 8/15/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	QT IRT – 5/8/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☐ 7/28/17
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ 7/19/17
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review See multidisciplinary review dated 8/15/17
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review 8/14/17; See multidisciplinary review dated 8/15/17
Statistical Review(s) *(indicate date for each review)*	☒ No separate review 8/11/17; See multidisciplinary

	review dated 8/15/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	7/28/17; See multidisciplinary review dated 8/15/17
Clinical Pharmacology review(s) *(indicate date for each review)*	7/28/17; See multidisciplinary review dated 8/15/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	8/11/17; See multidisciplinary review dated 8/15/17
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	7/5/17; 8/1/17; See multidisciplinary review dated 8/15/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ N/A
❖ ECAC/CAC report/memo of meeting	☒ N/A Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None 7/28/17
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None ; 7/25/17 (Facility) ; 7/24/17 (Process); 7/21/17 (Biopharmaceutics); 7/11/17 (drug product); 7/10/17 (drug substance); 7/11/17 (labeling)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Quality Review 7/28/17
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 7/25/2017 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done **N/A**
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

---

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/s/

CHRISTY L COTTRELL
08/18/2017

From:	Venugopal, Rajesh
To:	Chlysta, Lori A (lori.chlysta@astrazeneca.com); McCullough, Karen
Subject:	NDA 208558 (olaparib) - A third PMC request
Date:	Monday, August 14, 2017 6:40:41 AM
Attachments:	image001.png
Importance:	High

Hello Lori/Karen,

The following is a third PMC that the Agency want to see conducted. This is what today's teleconference discussion will be about. We wanted to send this to you in advance of the call today. Could you please put in appropriate milestones and send back before the call. We can cancel the call if there are no questions about it and if we are fine with the milestone dates.

PMC Description: 3238-3	Submit the overall survival (OS) analyses with datasets from clinical trial D0818C00002, SOLO-2, the ongoing randomized double-blind, placebo-controlled, multi-center trial to assess the efficacy of olaparib maintenance monotherapy in relapsed high grade serous ovarian cancer (HGSOC) patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function)) who have responded following platinum-based chemotherapy.

PMC Schedule Milestones:

Trial Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

rajesh
Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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/s/

RAJESH VENUGOPAL
08/14/2017

From:	Venugopal, Rajesh
To:	Chlysta, Lori A (lori.chlysta@astrazeneca.com); McCullough, Karen
Subject:	NDA 208558 (Olaparib) - Clinical Information Request
Date:	Thursday, August 10, 2017 11:16:36 AM
Attachments:	image001.png

Hello Lori,

Our clinical review team has the following information request requiring a response. Please respond as soon as possible today:

You should explain the rationale for the order of "most common adverse events (=20%)" and "most common laboratory abnormalities (= 25%)" in the Highlights section of the label. The chronology does not appear to be entirely based upon frequency, as described in Section 6 of the label (tables for Study 19 and SOLO2), but it is not clear. Explain how the ordering in the Highlights section was decided upon.

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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/s/

RAJESH VENUGOPAL
08/10/2017

From: Venugopal, Rajesh
To: Chlysta, Lori A (lori.chlysta@astrazeneca.com); McCullough, Karen
Subject: NDA 208558 (olaparib) - Information Request
Date: Wednesday, August 09, 2017 1:01:22 PM
Attachments: image001.png

Hi Lori,

Our review team has the following information request that require your response. Please respond by 12 PM tomorrow.

1) [redacted] (b) (4) updated label for the capsule, FDA would like to instead modify the original submission for supplement 7 (retaining your addition, section 6.2, postmarketing experience) and add only those sections in the Highlights, section 2.2, and the Medication Guide that contain warnings about the lack of interchangeability between capsule and tablet formulations. Part of the risk mitigation strategy that FDA foresaw was providing prescribers and patients with information regarding this lack of capsule formulation interchangeability simultaneously with the tablet approval. Therefore, this abbreviated labeling change for this purpose would be approved at the time of the tablet action. [redacted] (b) (4)

2) During the telcon with AZ discussing your June 2, 2017 risk mitigation strategy for the introduction of the tablet formulation under the same proprietary name, the Agency notes that you discussed the possibility of removing the capsule formulation from the market within [redacted] (b) (4) of the introduction of the tablet. Can you confirm that this is indeed the case?

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
08/09/2017

From: Venugopal, Rajesh
To: "Chlysta, Lori A"; McCullough, Karen
Subject: RE: NDA 208558 (olaparib) - revised PMCs for review - Information Request
Date: Wednesday, August 09, 2017 10:22:48 AM
Attachments: image001.png

Hi Lori. Information request for you re: the PMCs. Please respond by 12 PM tomorrow.

Based on (b) (4) Agency input on the protocol/SAP, propose new earlier dates for the trial completion. The Final report should be sent 6 months post trial completion. Provide a rationale/justification for the dates.

rajesh
Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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FDA U.S. FOOD & DRUG ADMINISTRATION

From: Chlysta, Lori A [mailto:lori.chlysta@astrazeneca.com]
Sent: Wednesday, August 09, 2017 8:33 AM
To: Venugopal, Rajesh; McCullough, Karen
Subject: RE: NDA 208558 (olaparib) - revised PMCs for review

Hello Rajesh,

Here are the new milestone dates (in red) for the SOLO3 PMC. All other dates are confirmed.

PMC Description: 3238-2	Submit the overall response rate (ORR) and duration of response (DOR) analyses with datasets from clinical trial D0816C00010: (SOLO3), entitled "a randomized trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations".	
PMR/PMC Schedule Milestones:	-	- -
	Draft Protocol (Amendment) Submission:	10/2017
	Draft Statistical Analysis Plan Submission:	11/2017
	Final Protocol Submission	12/2017

	Trial Completion	03/2020
	Final Report Submission	06/2020

This response will also be submitted to the NDA via the Gateway shortly. Please let us know if you have questions.

Best regards,

Lori Chlysta, MSc, RAC (US)
Regulatory Affairs Associate Director

AstraZeneca Pharmaceuticals LP
GMD | Regulatory Project Management
200 ORD, 3312A, Gaithersburg, MD
Tel +301 398 0636
mailto:lori.chlysta@astrazeneca.com

Please consider the environment before printing this e-mail

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, August 07, 2017 6:10 PM
To: Chlysta, Lori A <lori.chlysta@astrazeneca.com>; McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (olaparib) - revised PMCs for review

Hello Lori/Karen,

Below please find our revised 2 PMCs for olaparib as per our teleconference discussion this morning for your agreement. Please confirm and/or provide milestone date for each time point data will be submitted.
Please respond by 9 AM Wednesday August 9:

PMC Description: 3238-1	Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report, labeling, and datasets from clinical trial D0816C00020, entitled, "OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy."

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	08/07/2017
	Final Protocol Submission	11/07/2017
	Trial Completion:	12/01/2020

	Final Report Submission:	06/2021

PMC Description: 3238-2	Submit the overall response rate (ORR) and duration of response (DOR) analyses with datasets from clinical trial D0816C00010: (SOLO3), entitled " a randomized trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations".

PMR/PMC Schedule Milestones:	-	-	-
	Draft Protocol (Amendment) Submission:		MM/YYYY
	Draft Statistical Analysis Plan Submission:		MM/YYYY
	Final Protocol Submission		MM/YYYY
	Trial Completion		03/2020
	Final Report Submission		06/2020

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
08/09/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 7, 2017

Application Number: NDA 208558
Product Name: Lynparza™ (olaparib)
Sponsor/Applicant Name: AstraZeneca

Subject: Discussion of Agency Proposed PMCs

FDA Participants
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1 (via phone)
Sanjeeve Balasubramaniam, MD, Acting Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1 (via phone)
Jason Schroeder, PhD, Associate Director, Team Leader Biostatistics, OB/DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1
Katherine Fedenko, MS, CRNP, Deputy Director for Safety (DDS), DOP1

Sponsor/Applicant Participants
Hesham Abdullah, MD, MSc, RAC – VP, Regulatory Affairs, Oncology
Deborah Mackenzie, MS - Senior Director, Regulatory Affairs, Oncology
Karen McCullough, PhD – Director, Regulatory Affairs
Mika Sovak, MD PhD – Executive Clinical Director, Oncology
Tsveta Milenkova,MD - Clinical Filing Lead
Elizabeth Lowe – Clinical Scientist
David Cartwright – Associate Director, Clinical Development
Antony Sabin, MS – Senior Director/Team Lead, Biostatistics, Oncology
Ralph Bloomfield, MSc - Principal Statistician, Biostatistics, Oncology

BACKGROUND: On July 24, 2017, the Agency submitted to AstraZeneca (AZ) 3 Post Marketing Commitments for NDA 208558 for their review and agreement:

PMC Description (3238-X): Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report with datasets from clinical trial D0816C00020, entitled, "OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy."

PMR/PMC Schedule Milestones: Trial Completion: 09/01/2020
Final Report Submission: 03/2021

Reference ID: 4136203

[redacted]

PMC Description (3238-X): Submit [redacted] datasets from clinical trial D0816C00010 (SOLO3), a randomized trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline BRCA1/2 mutations.

PMR/PMC Schedule Milestones: Trial Completion: 03/2020
Final Report Submission: 06/2020

AZ responded by questioning whether the [redacted] and SOLO3 studies described above are required. The teleconference was held to further discuss whether two of the 3 PMCs are required.

DISCUSSION: AstraZeneca believes that [redacted] should not be a PMC for NDA 208,558. [redacted]

After further discussion the Agency decided to eliminate the PMC [redacted], and revise the PMC for the OPINION study: add additional milestone dates regarding SAP, draft protocol, and final protocol to better understand the effect of olaparib maintenance in the gBRCA wildtype subgroup.

[redacted] AZ provided options for the modification of the SOLO3 trial design [redacted] The Agency agreed to have AZ change SOLO3's open-label design to ORR and DOR as the primary endpoints [redacted]

(b) (4) The Agency has requested to evaluate the modified statistical analysis plan.

The Agency discussed with the Applicant that we will not include (b) (4) data in the label as it is not appropriate to include results with a large impact from informative censoring. The Applicant agreed.

ACTION ITEMS: The Agency to send revised PMCs for the OPINION and SOLO3 studies for the Applicant to review and commit to.

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/s/

RAJESH VENUGOPAL
08/08/2017

From: Venugopal, Rajesh
To: Chlysta, Lori A (lori.chlysta@astrazeneca.com); "McCullough, Karen"
Subject: NDA 208558 (olaparib) - revised PMCs for review
Date: Monday, August 07, 2017 6:10:18 PM
Attachments: image001.png

Hello Lori/Karen,

Below please find our revised 2 PMCs for olaparib as per our teleconference discussion this morning for your agreement. Please confirm and/or provide milestone date for each time point data will be submitted.
Please respond by 9 AM Wednesday August 9:

PMC Description: 3238-1	Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report, labeling, and datasets from clinical trial D0816C00020, entitled, "OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy."	
PMR/PMC Schedule Milestones:	Draft Protocol Submission:	08/07/2017
	Final Protocol Submission	11/07/2017
	Trial Completion:	12/01/2020
	Final Report Submission:	06/2021

PMC Description: 3238-2	Submit the overall response rate (ORR) and duration of response (DOR) analyses with datasets from clinical trial D0816C00010: (SOLO3), entitled " a randomized trial establishing the superiority of olaparib over physician's choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations".	
PMR/PMC Schedule Milestones:	-	- -
	Draft Protocol (Amendment) Submission:	MM/YYYY
	Draft Statistical Analysis Plan Submission:	MM/YYYY
	Final Protocol Submission	MM/YYYY
	Trial Completion	03/2020

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
08/07/2017

From:	Venugopal, Rajesh
To:	"Chlysta, Lori A (lori.chlysta@astrazeneca.com)"; "McCullough, Karen"
Subject:	RE: NDA 208558 (olaparib) - label
Date:	Monday, August 07, 2017 5:41:43 PM
Attachments:	Received from Sponsor_annotated-draft-label_8.2.17_Sent to Sponsor 8.7.17.pdf Received from Sponsor_annotated-draft-label_8.2.17_Sent to Sponsor 8.7.17.docx image001.png
Importance:	High

Hello Lori/Karen,

I am sorry for the confusion but we made 1 slight edit to the tablet label. A p=calue was slightly changed in section 14 because OHOP's best labeling practice is to use a maximum of 4 decimals when reporting p-values. Please use this attached label to finalize and send back.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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U.S. FOOD & DRUG ADMINISTRATION

From: Venugopal, Rajesh
Sent: Monday, August 07, 2017 3:05 PM
To: Chlysta, Lori A (lori.chlysta@astrazeneca.com); 'McCullough, Karen'
Subject: NDA 208558 (olaparib) - label

Hello Lori,

Attached please find our comments to the olaparib tablet label. If you approve, please finalize and send back by 9 am Wednesday August 9.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
08/07/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - Label
Date:	Friday, July 28, 2017 2:44:13 PM
Attachments:	image001.png Sent to Sponsor 7.28.17_annotated-draft-label.docx Sent to Sponsor 7.28.17_annotated-draft-label.pdf

Hi Karen,

Please see further edits to the label. We are fine with the immediate container label that was submitted on July 21. If you are okay with the edits and comments that are made then please accept the changes and email me a clean copy of the label and submit it through the gateway as well by 12 PM Wednesday August 2.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/28/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - Clinical Information Request
Date:	Wednesday, July 26, 2017 8:41:56 AM
Attachments:	image001.png

Hello Karen,

The information on financial interests for SOLO2 provided in the submission is not in a format conducive to the review process. You should provide us with the total number of investigators and subinvestigators participating in the SOLO2 study. Provide us with how many of these investigators and sub-investigators are/were employees (either full- or part-time) of AZ. Finally, provide the total number of SOLO2 investigators and subinvestigators with certification of due diligence in pursuing disclosable financial interests.

Please respond by 10 am tomorrow 7/27, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/26/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: NDA 208558 (Olaparib) - Clinical Information Request
Date: Monday, July 24, 2017 1:24:29 PM
Attachments: image001.png

Karen

The following is an information request form our clinical group. Please provide this information by 10 am tomorrow morning 7/25.:

Based upon the discrepancy between the FDA and AZ assessments of MDS/AML cases in the olaparib database, we request that you provide us with two tables (from your label comments).

1) Provide one table to show which 21 patients (patient ID numbers, study numbers, treatment arm) in which trials you have included (to give the 21 out of 1680 cases).
2) Provide an additional table to depict the (b) (4) cases (specific patient ID numbers, study numbers, and treatment arm) out of (b) (4) patients you have referenced.

Study #	Patient ID	Study arm

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/24/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Cc: Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject: NDA 208558 (Olaparib) - Post Marketing Commitments
Date: Monday, July 24, 2017 1:04:45 PM
Attachments: image001.png

Hi Karen,

We have the following 3 Post Marketing Commitments for your NDA for your review and that requires agreement from your group:

PMC Description: 3238-X	Submit the progression-free survival (PFS) and molecular characteristics (patient and tumor) final report with datasets from clinical trial D0816C00020, entitled, "OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non- Germline BRCA mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy."

PMR/PMC Schedule Milestones:

Trial Completion:	09/01/2020
Final Report Submission:	03/2021

(b) (4)

[redacted]

PMC Description: 3238-X	Submit the (b) (4) [redacted] datasets from clinical trial D0816C00010 (SOLO3), a randomized trial establishing the superiority of olaparib over physician's

	choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying deleterious or suspected deleterious germline *BRCA1/2* mutations.		
PMR/PMC Schedule Milestones:	-	-	-
	Trial Completion:		03/2020
	Final Report Submission:		06/2020

Please confirm and/or provide milestone date for each time point data will be submitted. Please respond via email by 12 PM Monday July 31, 2017 (if not sooner), with a proposal of the date for each milestone above.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/24/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 208558 (Olaparib) - Revisions/comments to Label
Date:	Wednesday, July 19, 2017 8:17:08 AM
Attachments:	image001.png

Hello Karen,

DOP1's best labeling practice is to use laboratory abnormalities in Section 6 (b) (4) (e.g., on study lab abnormalities).

We have reviewed results for olaparib's laboratory abnormalities for SOLO2 (Table 2) and Study 19 (Table 4) using both methodologies. In these cases, we believe that calculating the on study laboratory abnormalities provides the most relevant, precise, and accurate clinical experience for these trials.

rajesh
Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Monday, July 17, 2017 2:55 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Olaparib) - Revisions/comments to Label

Hi Rajesh,

In preparing revised labeling based on FDA's comments, our team had a question. Tables 2 and 4 correspond to lab abnormalities for SOLO2 and Study 19, respectively. (b) (4)

(b) (4)

(b) (4)

Thank you for the input,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, July 14, 2017 11:23 AM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (Olaparib) - Revisions/comments to Label

Hi Karen,

Upon review of the olaparib label you sent on July 5, 2017, the Agency has further revisions and comments to the PI for your team's review as well as comments/edits made to the medication guide. In addition, our CMC group ask the following sentences to be added to the container label regarding storage conditions. The storage conditions on the bottle labels do not align with the language in Section 16 of the PI. Please add the following to the container label:

"Store at 20ºC to 25ºC (68°F to 77°F), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture."
If you are okay with any and all of the edits and comments that we have made then please accept the changes and email me a clean copy of the label and submit it through the gateway as well.

Please respond by 3 PM Thursday July 20, 2017.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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/s/

RAJESH VENUGOPAL
07/19/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: NDA 208558 (Olaparib) - Clinical Information Request
Date: Friday, July 14, 2017 5:06:54 PM
Attachments: image001.png

Hi Karen,

Another information from our group:

We note that patient E2307511 (olaparib arm) on SOLO2 is listed in the AE dataset (from the safety update) as having experienced a serious adverse event of a plasma cell myeloma, however, this patient is not listed as a patient experiencing an event of new primary malignancy in Section 8.2.3.2 in the CSR. You will need to provide the case report form for this patient as well as a narrative for this patient (since it is an SAE) for our review.

Please provide this information by 10 am Tuesday 7/18/17.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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/s/

RAJESH VENUGOPAL
07/14/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Subject:	NDA 208558 (Olaparib) - Revisions/comments to Label
Date:	Friday, July 14, 2017 11:22:55 AM
Attachments:	image001.png olaparib (Lynparza) NDA 208558 DMPP-OPDP MG JUL-14-2017 marked.docx olaparib (Lynparza) NDA 208558 DMPP-OPDP MG JUL-14-2017 marked.pdf annotated-draft-label_Sent 7.14.17.doc annotated-draft-label_Sent 7.14.17.pdf draft-bottle-label-150mg-60tablets-clean_Sent to Sponsor 7.14.17.pdf draft-bottle-label-150mg-120tablets-clean_Sent to Sponsor 7.14.17.pdf draft-bottle-label-100mg-60tablets-clean_Sent to Sponsor 7.14.17.pdf draft-bottle-label-100mg-120tablets-clean_Sent to Sponsor 7.14.17.pdf

Hi Karen,

Upon review of the olaparib label you sent on July 5, 2017, the Agency has further revisions and comments to the PI for your team's review as well as comments/edits made to the medication guide. In addition, our CMC group ask the following sentences to be added to the container label regarding storage conditions. The storage conditions on the bottle labels do not align with the language in Section 16 of the PI. Please add the following to the container label:

"Store at 20ºC to 25ºC (68°F to 77°F), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store in original bottle to protect from moisture."
If you are okay with any and all of the edits and comments that we have made then please accept the changes and email me a clean copy of the label and submit it through the gateway as well.

Please respond by 3 PM Thursday July 20, 2017.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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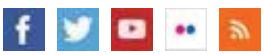

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/s/

RAJESH VENUGOPAL
07/14/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Subject:	NDA 208558 (Olaparib) - Clinical Information Request
Date:	Friday, July 14, 2017 10:35:23 AM
Attachments:	image001.png

Hi Karen,

Our Clinical team has the following information request that requires a response:

We note that Patient E4304505 on the olaparib arm of SOLO2 was diagnosed with 2 malignancies, reported as adverse events in the AE dataset. These included gastric cancer and malignant lymphoma. A narrative account of the gastric cancer diagnosis was provided in section 8.2.3.2 of the CSR, but there is not mention of the lymphoma diagnosis, nor was this listed as one of the new primary malignancies described in that section. Provide an explanation for your exclusion of the lymphoma event as a case of secondary malignancy, and provide a narrative description of this adverse event in this patient, given that it appears to be separate from the event of gastric cancer (different dates of onset in the AE dataset, etc).

Please provide the response by 12 PM on Monday 7/17.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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Office of Hematology and Oncology Products
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RAJESH VENUGOPAL
07/14/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: NDA 208558 (Olaparib) - Clinical information request
Date: Wednesday, July 12, 2017 1:23:34 PM
Attachments: image001.png

Hi Karen,

Please the table below. Our review team needs the last column (highlighted) filled out by your team as soon as possible but no later than 2 PM tomorrow.

Study	Indication	Number exposed to olaparib 300 mg BID tablets	Number of patients with ovarian cancer
SOLO2	Phase 3 advanced ovarian cancer	195	195
Study 24	Phase I bioavailability study in advanced solid tumors (groups 4 and 6)	24	
Study 4	Phase I food effect and QT study in advanced solid tumors	57	
Study 7	Phase I PK study with CYP inhibitor in advanced solid tumors	56	
Study 8	Phase I PK study with rifampin in advanced solid tumors	19	
Study D081BC00001	Phase I dose escalation study in Japanese patients with advanced solid tumors	19	
Study D081CC00001	Phase I anti-hormonal PK study of olaparib	69	
Study 6	Phase I renal impairment study of olaparib	43	
Total		482	

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/12/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Subject:	NDA 208558 (Olaparib) - Clinical Information Request
Date:	Monday, July 10, 2017 12:20:56 PM
Attachments:	image001.png

Hi Karen,

Our clinical review team has the following information request requiring your response:

There appear to be 7 patients (6 olaparib and 1 placebo) who had protocol deviations due to not meeting the following criterion:

Patients who have received at least 2 prior lines of platinum containing therapy prior to randomization and met further conditions of those therapies.

The patients are as follows:
olaparib: E1003503, E2310501, E2310503, E2310504, E7007510, E7803503;
placebo: E1001504.

Please provide descriptions for how/why these patients failed to meet this inclusion criterion (particularly since CRFs are not available for any of these patients). Also explain why these particular deviations are not thought to have impacted study results in any way.

Please respond by 10 AM tomorrow July 11, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
07/10/2017

TELECONFERENCE PRELIMINARY TALKING POINTS

Meeting Date	Tuesday, May 9, 2017
Time:	10:00 AM – 11:00 AM
Meeting Location:	White Oak Building 22, Room 4270
Application Number:	NDA 208558
Product Name and Strength:	Lynparza (olaparib) Tablets, 100 mg and 150 mg
Applicant/Sponsor Name:	AstraZeneca
Call-In Information:	Toll Free: (b) (4) Conference Code: (b) (4)
Meeting Chair:	Danielle Harris, PharmD, BCPS, Acting Deputy Director
FDA Participants:	Division of Medication Error Prevention and Analysis (DMEPA) Tingting Gao, PharmD, Safety Evaluator Chi-Ming (Alice) Tu, PharmD, Team Leader Danielle Harris, PharmD, BCPS, Acting Deputy Director Maximilian Straka, PharmD, DMEPA ISMP Fellow Office of Surveillance and Epidemiology (OSE) Frances Fahnbulleh, PharmD, Safety Regulatory Project Manager Division of Oncology Products 1 (DOP1) Gwynn Ison, MD, Clinical (efficacy reviewer) Runyan Jin, PhD , Clinical Pharmacology Reviewer Jingyu (Jerry) Yu, PhD, Pharmacometrics Team Leader Chao Liu, PhD, Pharmacometrics Reviewer Olen Stephens, PhD, Chemistry Reviewer - Drug Product Rajesh Venugopal, MPH, MBA, Regulatory Health Project Manager Division of Medical Policy Programs (DMPP) Sharon Mills, BSN, RN, CCRP, Patient Labeling Reviewer
Sponsor Participants:	AstraZenca Karen McCullough (me) – Director, Regulatory Affairs Debbie Mackenzie – Senior Director, Global Regulatory Affairs Simon Turner – Principle Pharmacovigilance Scientist Mika Sovak – Executive Clinical Director, Oncology Tsveta Milenkova – Medical Director, Oncology Jim Blasetto – VP Evidence Generation Sean Zhao – Head of US Patient Safety

Reference ID: 4120744

Sponsor Participants Cont'd:
Brian Burns – Associate Director, Women's Cancer Franchise
Dave Satre – Director, Access Strategy
Maria Learoyd – Senior Clinical Pharmacology Scientist
Hesham Abdullah – VP, Regulatory Affairs

BACKGROUND:

Lynparza (olaparib) Capsule was approved on December 19, 2014 under NDA 206162. The Applicant submitted the name, Lynparza, for a new tablet dosage form, for review under NDA 208558 on February 27, 2017.

MEETING OBJECTIVES:

The purpose of this teleconference is to notify AztraZeneca of our preliminary findings for the proposed proprietary name, Lynparza, for the olaparib tablet formulation.

Based on the information contained within the February 27, 2017 submission, DMEPA finds that the tablet formulation of olaparib cannot safely co-exist under the same exact proprietary name as the currently marketed capsule formulation. We find that, as proposed, use of the same proprietary name is likely to result in medication errors related to indiscriminate switching between the currently marketed capsule formulation and the proposed tablet formulation, and vice versa. We are concerned that prescriptions for Lynparza are unlikely to contain enough information to signal to the pharmacist which formulation is intended to be dispensed, as prescriptions may not always include a dosage form or strength provided provide the dose is include (e.g., Lynparza 300 mg PO BID). We note that the proposed doses for the tablet formulation are achievable using the proposed capsule formulation strengths, and vice versa. In other words, a prescription for Lynparza 300mg BID, for example, could be filled by a pharmacist with either formulation without identifying a need to clarify with a prescriber which formulation is intended. Therefore, a prescription intended to be dispensed with tablets, may inadvertently be filled with capsules, or vice versa, especially if the prescriber or pharmacist is unaware that multiple formulations are available for use, or if they are not aware that the formulations are not interchangeable.

We acknowledge AztraZeneca's proposed mitigation strategies, (b) (4) however, we find these strategies alone to be insufficient to mitigate the potential for error.

Furthermore, based on the Failure Mode and Effects Analysis (FMEA) included in the aforementioned submission, it appears that confusion between capsule and tablet formulations may result in ***overdoses*** resulting in potential hematologic toxicity (e.g. anemia, thrombocytopenia, neutropenia), and increased frequency and/or severity of adverse effects, or ***underdoses*** resulting in decreased therapeutic efficacy. Based upon your conclusions from your FMEA, these events may result in potential patient harm, require monitoring and supportive care, including transfusions, and treatment with erythropoiesis stimulation agents, and granulocyte colony stimulating factors.

Additionally, in response to our information request, AztraZeneca confirmed their intention for both formulations to co-exist fo (b) (4) .

Tcon Discussion:
DMEPA presented our aforementioned concerns (See Meeting Objectives above). AstraZeneca (AZ) responded by describing the current distribution model for the capsules, and then further stated that the capsules will be distributed via 2 specialty pharmacies. AZ also stated they have high visibility of Lynparza prescribers. After few exchanges of questions and answers between DMEPA, DOP1, and AZ, the proposed distribution model of Lynparza capsules and the proposed tablets was still unclear so we requested AZ to submit a written documentation to address our concerns. This documentation should include the information AZ provided about the limited number of anticipated prescribers and specifics about the proposed distribution channel. Additionally, we asked AZ to provide their evaluation on the use of a modifier (i.e., Lynparza + modifier) as a means for differentiating the proposed tablets.
The sponsor agreed to provide the information via email by Friday May 12, 2017, followed by submission to the NDA as an amendment to the proprietary name request.

The email was received on May 15, 2017 by Frances Fahnbulleh, OSE SRPM and the amendment was submitted to the NDA on May 16, 2017.

The Teleconference ended at 11:00 AM, EST.

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FRANCES G FAHNBULLEH
07/06/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 208558 (olaparib) - Revised Label
Date:	Wednesday, June 28, 2017 3:52:55 PM
Attachments:	image001.png

Hi Karen,

Please see below our clinical reviewer's response to your questions re: the tables in the label:

Olaparib label- AE terms:

Table 1- SOLO2 AEs. AE dataset (ADAE with N (b) (4) patients experiencing AE). Note: In the dataset, EPOCH included TREATMENT and FOLLOW-UP.

Preferred terms used in calculating FDA number of AEs reported in proposed table are as follows:

Anemia- included anemia, hematocrit decreased, hemoglobin decreased, iron deficiency, red cell decreased, mean cell volume increased.
Diarrhea- included diarrhea, colitis, feaces soft
(b) (4)
Stomatitis- included abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection/ inflammation, oral candidiasis, oral discomfort, oral herpes, oral infection, oral mucosal erythema, oral pain, oral pharyngeal discomfort/ pain
Nasopharyngitis/URI/Sinusitis/Rhinitis, influenza- only included these 4 terms combined together.
Arthralgia/myalgia- included arthralgia, myalgia, muscle twitching, musculoskeletal pain, muscle spasms, limb discomfort, joint stiffness, arthritis, osteoarthritis, joint swelling, musculoskeletal stiffness
Headache – included headache, migraine, and migraine with aura.

Table 3- Study 19 AEs.

AE dataset from original NDA 206162 submission.- selected TRTEMFL= Y
Anemia- also includes anemia macrocytic, hematocrit decreased, hemoglobin decreased, iron deficiency, macrocytosis, red cell count decreased, reticulocytosis
Nausea- only nausea
(b) (4)
Vomiting- only vomiting
Diarrhea- also includes abnormal feces and fecal incontinence
Constipation- also subileus
Fatigue – combined with asthenia
Respiratory tract infection- included respiratory tract infection, resp. tract infection viral, bronchitis, laryngitis, lower respiratory tract infection, rhinitis, sinusitis, URI

Headache- headache and migraine with aura

Table 5:

Nasopharyngitis/URI- included- URI, pharyngitis, viral uri, respiratory tract infections, rhinitis, allergic rhinitis, rhinorrhea, sinus congestion, respiratory disorder, pulmonary congestion, strep pharyngitis, sinusitis, rhinitis seasonal, upper resp tract congestion
Arthralgia/ musculoskeletal pain- in addition to arthralgia and musculoskeletal pain, included pain in extremity, joint stiffness, musculoskeletal chest pain, joint swelling, arthritis, musculoskeletal stiffness
Myalgia included: includes pain in extremity, joint stiffness, musculoskeletal chest pain, joint swelling, arthritis, musculoskeletal stiffness

Table 2:

(b) (4)

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Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Wednesday, June 28, 2017 10:26 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (olaparib) - Revised Label

Hi Rajesh,

Here is a more specific request from the clinical/safety team:

We cannot get the data for the frequencies for the following terms in the FDA's proposals for the tablets USPI to match with the corresponding data in the outputs provided in the NDA:

Table 1: Anemia, diarrhea, (b) (4), stomatitis, nasopharyngitis/URI/sinusitis/rhinitis/influenza, arthralgia/myalgia and headache
Table 3: Anemia, nausea, (b) (4), vomiting, diarrhea, constipation, fatigue (including asthenia), respiratory tract infection, headache
Table 5: Nasopharyngitis/URI, arthralgia/musculoskeletal pain, myalgia

We do not know whether this is because FDA has grouped terms together (and we don't know which terms), or if there are discrepancies between the datasets we are using and they are using.

In terms of labs (**Table 2** only), we cannot replicate any of the values and aren't sure what assumptions were used to produce these data, or again, if the datasets they used are different from ours.

Thank you in advance for any input you can provide us.

Best,
Karen

From: McCullough, Karen
Sent: Wednesday, June 28, 2017 9:14 AM
To: 'Venugopal, Rajesh' <Rajesh.Venugopal@fda.hhs.gov>
Cc: Chlysta, Lori A <lori.chlysta@astrazeneca.com>
Subject: RE: NDA 208558 (olaparib) - Revised Label

Hi Rajesh- confirming receipt, we'll get the list to you soon.
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, June 27, 2017 9:50 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Cc: Chlysta, Lori A <lori.chlysta@astrazeneca.com>
Subject: RE: NDA 208558 (olaparib) - Revised Label

Hello Karen,

Please provide me with a list of the specific AEs that you have conflict with in Tables 1, 3, and 5, and we can provide you with the terms that were used to derive our values.

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Tuesday, June 27, 2017 6:12 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (olaparib) - Revised Label

Hi Rajesh,

The team is working through the Agency's comments on the USPI, and have some questions about the proposed changes to tables in Section 6. We are thinking that some of the differences in values in tables in this section arise from different strategies for grouping preferred terms.

Would it be possible for the reviewers to let us know what terms have been grouped in Tables 1, 3 and 5 for any AE that includes multiple preferred terms (PTs)?

Thank you for the input,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, June 27, 2017 8:34 AM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (olaparib) - Revised Label

Hello Karen,

Attached please find the Agency's edits and comments for the PI and below edits for the container label. Please note that Section 17 and the medication guide are still under review and will be provided to you in 2-3 weeks, if not sooner. Please let me know if you find the changes acceptable by 3 PM Wednesday July 5.

A. Container labels

1. The NDC numbers are presented as a placeholder "XXXX-XXXX-XX". Ensure that the product codes (the middle 3 digits -XXX-) in the NDC numbers are non-sequential between the product strengths. Assignment of sequential numbers for product codes is not an effective differentiating feature (e.g. -666-, -667-, and -668-), which may lead to selecting and dispensing of wrong drug.
2. Relocate the net quantity statement ("60 Tablets" and "120 Tablets") away from the strength so that it does not compete for prominence with the strength statement and minimize the risk of numerical confusion between the strength and net quantity. This can be achieved by relocating the net quantity statement to immediately below the "Attention: Lynparza Tablets and Capsules…" statement.
3. Revise the statement "Attention: Lynparza Tablets and Capsules are NOT (b) (4) Do NOT take more than 4 Tablets a day." to read "Attention: Lynparza Tablets and Capsules are NOT substitutable. Do NOT take more than 4 Tablets a day." because the term "(b) (4) refers to biosimilar products, thus making the proposed Lynparza Tablet that is not a biosimilar product misleading. Additionally, add a rectangular outline around the text to increase its prominence.
4. Remove the (b) (4)" statement since it is not required per 21 CFR 201.100(b)(3) for oral products and to reduce information crowding on the principal display panel.
5. The storage statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that the acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality. Ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges. For example, revise "15-30°C" to read "15°C - 30°C".

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
06/28/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: NDA 208558 (olaparib) - Revised Label
Date: Tuesday, June 27, 2017 8:34:04 AM
Attachments: Sent to Sponsor_6.27.17_Submitted 2.22.17_annotated-draft-label.pdf
Sent to Sponsor_6.27.17_Submitted 2.22.17_annotated-draft-label.doc
image001.png

Hello Karen,

Attached please find the Agency's edits and comments for the PI and below edits for the container label. Please note that Section 17 and the medication guide are still under review and will be provided to you in 2-3 weeks, if not sooner. Please let me know if you find the changes acceptable by 3 PM Wednesday July 5.

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Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
06/27/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 208558 (olaparib) - Revised Label
Date:	Tuesday, June 27, 2017 9:50:02 PM
Attachments:	image001.png

Hello Karen,

Please provide me with a list of the specific AEs that you have conflict with in Tables 1, 3, and 5, and we can provide you with the terms that were used to derive our values.
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Tuesday, June 27, 2017 6:12 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (olaparib) - Revised Label

Hi Rajesh,

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Would it be possible for the reviewers to let us know what terms have been grouped in Tables 1, 3 and 5 for any AE that includes multiple preferred terms (PTs)?

Thank you for the input,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, June 27, 2017 8:34 AM

To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (olaparib) - Revised Label

Hello Karen,

Attached please find the Agency's edits and comments for the PI and below edits for the container label. Please note that Section 17 and the medication guide are still under review and will be provided to you in 2-3 weeks, if not sooner. Please let me know if you find the changes acceptable by 3 PM Wednesday July 5.

A. Container labels

1. The NDC numbers are presented as a placeholder "XXXX-XXXX-XX". Ensure that the product codes (the middle 3 digits -XXX-) in the NDC numbers are non-sequential between the product strengths. Assignment of sequential numbers for product codes is not an effective differentiating feature (e.g. -666-, -667-, and -668-), which may lead to selecting and dispensing of wrong drug.
2. Relocate the net quantity statement ("60 Tablets" and "120 Tablets") away from the strength so that it does not compete for prominence with the strength statement and minimize the risk of numerical confusion between the strength and net quantity. This can be achieved by relocating the net quantity statement to immediately below the "Attention: Lynparza Tablets and Capsules…" statement.
3. Revise the statement "Attention: Lynparza Tablets and Capsules are NOT (b) (4) Do NOT take more than 4 Tablets a day." to read "Attention: Lynparza Tablets and Capsules are NOT substitutable. Do NOT take more than 4 Tablets a day." because the term "(b) (4) refers to biosimilar products, thus making the proposed Lynparza Tablet that is not a biosimilar product misleading. Additionally, add a rectangular outline around the text to increase its prominence.
4. Remove the (b) (4)" statement since it is not required per 21 CFR 201.100(b)(3) for oral products and to reduce information crowding on the principal display panel.
5. The storage statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that the acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality. Ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges. For example, revise "15-30°C" to read "15°C - 30°C".

Thank you,
rajesh
Rajesh Venugopal, MPH, MBA

Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
06/27/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: NDA 208558 (Olaparib) - Statistics Information Request
Date: Monday, June 26, 2017 7:29:22 AM
Attachments: image001.png

Hello Karen,

Our Stats review team has the following information request requiring your response:

Please send the SAS code used to generate the Table 11.2.10.3 in your SOLO2 CSR and explain the relevance of some quantities in your quality of life datasets (ADQS, RSQS):

1) What is the purpose of each of the following flags:ANL01FL, ANL02FL, ANL03FL, ANL04FL in datasets RSQS and ADQS.
2) Please submit the SAS program used to create Table 11.2.10.3 in SOLO2's CSR. In your response please include any datasets which were not submitted in your application.

Please respond by 3 PM Tuesday June 27, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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
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/s/

RAJESH VENUGOPAL
06/26/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 8, 2017

Application Number: NDA 208558
Product Name: Olaparib
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

Subject: Follow-up to May 18, 2017 Discussion of Current Indication and Application

FDA Participants
Richard Pazdur, MD, Director, OCE, Acting Director, OHOP
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Team Leader, DOP1
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Stella Karuri, PhD, Biostatistics Reviewer, OB/DBV
Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1

Sponsor/Applicant Participants
Hesham Abdullah, MD, MSc, RAC - VP, Regulatory Affairs, Oncology
Deborah Mackenzie, MS - Senior Director, Regulatory Affairs, Oncology
Karen McCullough, PhD - Director, Regulatory Affairs, Oncology
Klaus Edvardsen, MD – Senior VP, Head of Oncology, Global Medicines Development
Mika Sovak, MD PhD - Executive Medical Director, Oncology
Tsveta Milenkova, MD - Global Clinical Lead
Antony Sabin, MS – Senior Director/Team Lead, Biostatistics, Oncology
Tim French, PhD – Diagnostic Director Oncology
Sean Bohen, MD, PhD – EVP Global Medicines Development and CMO
Greg Rossi, PhD – Global Medicines Lead, Lynparza

BACKGROUND: AstraZeneca (AZ) submitted an NDA for a new tablet formulation of olaparib [NDA 208558 (olaparib) Tablets, 100 mg, 150 mg] for the maintenance treatment of patients with platinum-sensitive relapsed (PSR) ovarian cancer in response to platinum-based chemotherapy, regardless of BRCA mutation status, based on two pivotal studies, SOLO2 and Study 19.

This application is intended to provide confirmatory evidence that olaparib has an acceptable benefit:risk profile as a maintenance therapy in relapsed ovarian cancer. The applicant also requests that the ≥ third-line indication (currently approved for the capsule formulation) be given to the tablet formulation of olaparib and changed from accelerated to regular approval.

The NDA was submitted to the Agency via rolling submission in which the final piece of the submission was submitted on February 22, 2017. This is a non-NME priority review with a 6 month goal date of August 22, 2017.

Reference ID: 4110763

DISCUSSION: Upon reviewing AZ's position paper submitted on May 30, 2017, regarding their defense of their proposed indication for olaparib in maintenance treatment of PSR ovarian cancer, the Agency had a follow-up teleconference to discuss further the indication and the application as a whole.

The Agency proposed a potential PMC from AZ post approval of NDA 208558, for the planned Phase 3b, open-label, single-arm (b) (4) study (b) (4) The primary endpoint is PFS (investigator-recorded assessments according to modified RECIST v1.1). (b) (4)

On June 2, 2017, AZ provided the Agency with a risk mitigation strategy for Lynparza when introducing the tablet formulation to the U.S. market to prevent dosing errors. The Agency told AZ that the transition plan is acceptable, however, during the transition from moving from capsule to tablet formulation, the Agency emphasized to AZ to be mindful to prevent any issues of drug shortage, health insurance obstacles, and provide an option for drug availability should a few patents not follow the procedures for the formulation transition. The Agency suggested that AZ establish a phone number for patients on the capsule to call in an emergency if they are having trouble getting their prescription filled after the entire supply of olaparib capsules moves to the specialty pharmacies.

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/s/

RAJESH VENUGOPAL
06/13/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 25, 2017

Application Number: NDA 208558
Product Name: Olaparib
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

Subject: Clinical/Statisitics T-con with AZ

FDA Participants
Amna Ibrahim, MD, Deputy Director, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Stella Karuri, PhD, Biostatistics Reviewer, OB/DBV

Sponsor/Applicant Participants
Tony Sabin, MS, Senior Director/Team Lead, Biostatistics, Oncology
Ralph Bloomfield, MS, Statistical Science Director
Dan Graham, Associate Director, Statistical Programming
Mark Reynolds, Associate Director, Statistical Programming
Tsveta Milenkova, MD, Clinical Filing Lead
Mika Sovak, MD PhD, Executive Clinical Director, Oncology
Karen McCullough, PhD, Director, Regulatory Affairs
Debbie Mackenzie, MS, Senior Director Regulatory Affairs

BACKGROUND:

The Agency requested this meeting with AZ through WebEx as they are unable to verify the PFS endpoints reported for the SOLO2 study, based upon either INV or IRC assessments. An inability to confirm these data are approvability issues for this NDA. This WebEX discussion was provided by AZ so that the applicant can visually assist and direct the Agency to the various datasets requested in the application.

AstraZeneca submitted an NDA for a new tablet formulation of olaparib [NDA 208558 (olaparib) Tablets, 100 mg, 150 mg] for the maintenance treatment of patients with platinum-sensitive relapsed (PSR) ovarian cancer in response to platinum-based chemotherapy, regardless of BRCA mutation status, based on two pivotal studies, SOLO2 and Study 19.

This application is intended to provide confirmatory evidence that olaparib has an acceptable benefit:risk profile as a maintenance therapy in relapsed ovarian cancer. The Applicant also requests that the ≥ third-line indication (currently approved for the capsule formulation) be awarded to the tablet formulation of olaparib.

Reference ID: 4104744

The NDA was submitted to the Agency via rolling submission in which the final piece of the submission was submitted on February 22, 2017. This is a non-NME priority review with a 6 month goal date of August 22, 2017.

DISCUSSION:

The Agency and AZ reviewed and discussed the datasets in order to perform confirmation of INV assessment of PFS for the SOLO2 trial. The Agency has been unable to understand discrepancies between Agency analyses and the applicant's, which stem from irregularties in the analysis datasets

In addition, the IRC analysis datasets for PFS was discussed, including a request from the Agency for the applicant to provide a dataset that includes tumor measurements by IRC assessment for all patient scans, confirming the request from the email correspondence of May 19, 2017. This request includes providing measurements of all lesions, including non-target lesions, for all patients in addition to indicating whether new tumors were detected.

ACTION ITEMS:

Applicant to provide datasets based on the information requested (submitted on May 19, 2017). With these datasets, the Agency requested inclusion of the programs and the source columns from the eCRF, SDTM, and ADaM datasets that were used to populate the columns of the new datasets.

Reference ID: 4104744

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/s/

RAJESH VENUGOPAL
05/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Karen McCullough, PhD
Director, Global Regulatory Affairs Oncology

Dear Dr. McCullough:

Please refer to your New Drug Application (NDA) dated and received February 22, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olaparib Tablets, 100 mg and 150 mg.

We also refer to:

- your correspondence, dated and received February 27, 2017, requesting review of your proposed proprietary name, Lynparza
- and your amendment, dated and received May 16, 2017, to your request for name review

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

If any of the proposed product characteristics as stated in your above submissions 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 Rajesh Venugopal, Regulatory Project Manager in the Office of New Drugs at (301) 796-4730.

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/

TODD D BRIDGES
05/26/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 18, 2017

Application Number: NDA 208558
Product Name: Olaparib
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

Subject: Post Mid-Cycle – Discussion of Issues Concerning Application

FDA Participants
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Team Leader, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Qi Liu, PhD, Clinical Pharmacology Team Leader, OCP/DCPV
Runyan Jin, PhD, Clinical Pharmacology Reviewer, OCP/DCPV
Chao Liu, PhD, Pharmacometrics Reviewer, OCP/DCPV
Jingyu (Jerry) Yu, Pharmacometrics Team Leader, OCP/DCPV
Shenghui Tang, PhD, Biostatistics Team Leader, OB/DBV
Stella Karuri, PhD, Biostatistics Reviewer, OB/DBV
Todd Bridges, PhD, DMEPA Director
Chi-Ming (Alice) Tu, PharmD, DMEPA Team Leader
Sharon Mills, Pt. Labeling Reviewer DMPP
Barbra Fuller, Pt. Labeling Team Leader DMPP
Naomi Redd, DRISK, REMS reviewer

Sponsor/Applicant Participants
Hesham Abdullah, MD, MSc, RAC - VP, Regulatory Affairs, Oncology
Deborah Mackenzie, MS - Senior Director, Regulatory Affairs, Oncology
Karen McCullough, PhD - Director, Regulatory Affairs, Oncology
Mika Sovak, MD PhD - Executive Medical Director, Oncology
Tsveta Milenkova, MD - Global Clinical Lead
Ralph Bloomfield, MSc - Principal Statistician, Biostatistics, Oncology
Maria Learoyd, PhD – Associate Director Pharmacology

BACKGROUND: AstraZeneca submitted an NDA for a new tablet formulation of olaparib [NDA 208558 (olaparib) Tablets, 100 mg, 150 mg] for the maintenance treatment of patients with platinum-sensitive relapsed (PSR) ovarian cancer in response to platinum-based chemotherapy, regardless of BRCA mutation status, based on two pivotal studies, SOLO2 and Study 19.

This application is intended to provide confirmatory evidence that olaparib has an acceptable benefit:risk profile as a maintenance therapy in relapsed ovarian cancer. The Applicant also requests that the ≥ third-line indication (currently approved for the capsule formulation) be awarded to the tablet formulation of olaparib.

Reference ID: 4101880

The NDA was submitted to the Agency via rolling submission in which the final piece of the submission was submitted on February 22, 2017. This is a non-NME priority review with a 6 month goal date of August 22, 2017.

DISCUSSION:

1. The Agency expressed concerns about having both the capsule and tablet formulations, with the same Lynparza name, on the market simultaneously. The concern relates to the risk for medication errors, given that the 2 formulations are not interchangeable. The Agency proposed the following possible strategies to mitigate these concerns:
   a. Removing the capsules from the market immediately at the time of tablet approval, but providing the capsules to appropriate patients under an expanded access program.
   b. Having AZ provide a transition plan for patients to move t tablets from capsules upon approval of the tablet.
   c. Having a REMS in place for the tablet formulation
   d. Having AZ provide better oversight of the 2 specialty pharmacies who will be the sole distributors of the capsule formulation, once the tablet is approved.
   e. Alternatively, adding a boxed warning to the label, to further draw attention to the fact that capsules and tablets are not interchangeable.

2. The Agency notified AZ that they believe olaparib should only be indicated for patients with gBRCAm ovarian cancer who are in response to platinum based chemotherapy. It was conveyed that based upon the results of SOLO2, in combination with results from Study 19, there is not compelling data to support the proposed maintenance indication for patients with platinum-sensitive relapsed (PSR) ovarian cancer who do not have a documented gBRCA mutation. In response to this proposal, AZ stated that they intend to provide additional information to support including all-comers (ITT population) in the maintenance indication.

3. The Agency continues to have difficulty confirming the investigator assessed primary endpoint for SOLO2. Likewise the Agency has not been able to verify the IRC assessment of PFS due to missing data, (b) (4) AZ has asked to have a separate call with clinical and statistics to assist with dataset navigation and to help replicate their analyses of the investigator and IRC assessed primary endpoint. AZ also stated that they will submit data to conduct an analysis of the BICR assessment of PFS. They committed to submitting data on all patient lesions/ tumor measurements for FDA review.

ACTION ITEMS:

AZ requests another teleconference to review the IRC data with statistics and clinical.

Reference ID: 4101880

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/s/

RAJESH VENUGOPAL
05/23/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Cc: Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject: NDA 208558 (Olaparib) - Clinical Information Request
Date: Friday, May 19, 2017 12:43:33 PM
Attachments: image001.png

Hi Karen,

As was discussed during the T-con on 5/18/17, the clinical/ statistical team is still unable to verify the primary PFS endpoint reported for the SOLO2 study, based upon either INV or IRC assessments. An inability to confirm these data are approvability issues for this NDA. We have the following information requests for additional datasets which are essential for us to move forward with our analysis of this NDA.

1. **Confirmation of INV assessment of PFS.** We have identified 187 (63%) of patients who have no baseline tumor measurements by INV. This is in comparison to only 138 patients who were documented to be in CR at study baseline who may not have had measurable lesions at baseline in the dataset. Because of the apparent discrepancy and our lack of ability to understand the reason for the discrepancy based upon our analyses with the datasets, we are still unable to confirm your INV assessment of PFS.

Provide a detailed description of the discrepancy with rationale in a line-by-line patient listing. In addition, fill in and submit the below information for the 187 patients with non-measurable lesions at baseline:

Patient ID	Arm	Baseline tumor status (CR/PR)- include whether different analyzers may have coded some patients differently (INV, IRC, IVRS)	Baseline scan date	Baseline non-target lesions by INV? Y/N	Non-target lesion number and diameter (linking up to RSTU dataset)- give a separate row for EACH non-target lesion.	Scan date and findings on non-target lesions on that scan date (CR, PR, SD, PD) and non-target lesion diameter	New lesions on that date? Y/N	Overall tumor assessment by INV on that scan date- including target, non-target, new lesions (CR, PR, SD, PD)

2. IRC analysis datasets for PFS. Resubmit the IRC analysis datasets to include tumor measurements by IRC assessment for all patient scans, as communicated by FDA at the time of primary endpoint switch. The dataset should include measurements of all lesions, including non-target lesions, for all PR patients. In your dataset you should also indicate whether new tumors were detected. In the event that a measurement for a given lesion cannot be provided, a description for why a measurement is not possible should be given.

Please respond by 10 AM Friday May 26, if not sooner.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
05/19/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: RE: NDA 208558 - olaparib information request
Date: Thursday, May 18, 2017 9:19:22 AM
Attachments: image001.png

Hi Karen,

We acknowledge that there was an error made on our part on one of the IDs: We were able to find the following one that was requested, D0816C00002/E7001510, so we won't need that. However we neglected to include another one that we do need and don't have, which is:

1. D0816C00002/E0708503

So, please add this one to the list. It is fine that the CRFs will go beyond the database lock. We can wait til you can include lab data, so delivering them all tomorrow is fine.

Just to reconfirm, the ID numbers we need are as follows:

1. D0816C00002/E2301501
2. D0816C00002/E2307502
3. D0816C00002/E4304515
4. D0816C00002/E4304516
5. D0816C00002/E5003502
6. D0816C00002/E7001511
7. D0816C00002/E0708503

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Thursday, May 18, 2017 8:44 AM
To: Kim, Janice

Cc: Venugopal, Rajesh
Subject: RE: NDA 208558 - olaparib information request

Hi Rajesh,

The CRF for one of the patients below was submitted with the original NDA. We can't resubmit once the CRF has a home in the eCTD, so hopefully the reviewer can find it.

We are requesting CRFs for the rest of the patients. The problem is that we can't generate CRFs that only go up to database lock, so what we deliver will contain data that goes beyond this point.

The other complication is that I can only get CRFs without lab data by noon today. We can deliver CRFs with lab data tomorrow morning.

Hope that is acceptable.
Karen

From: Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
Sent: Wednesday, May 17, 2017 12:27 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Cc: Venugopal, Rajesh <Rajesh.Venugopal@fda.hhs.gov>
Subject: NDA 208558 - olaparib information request

Dear Ms. McCullough,

I am covering for RPM, Rajesh today. We have the following clinical information request:

You should submit the Case Report Forms for the following patients from SOLO2 for our review:

D0816C00002/E2301501

D0816C00002/E2307502

D0816C00002/E4304515

D0816C00002/E4304516

D0816C00002/E5003502

D0816C00002/E7001510

D0816C00002/E7001511

Please respond to this IR by tomorrow May 18, 2017 noon by email to facilitate review and by official submission to your NDA.

Thank you,

Janice

Janice Kim, PharmD, MS
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: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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RAJESH VENUGOPAL
05/18/2017

Kim, Janice

From: Kim, Janice
Sent: Wednesday, May 17, 2017 12:27 PM
To: 'Karen.McCullough@astrazeneca.com'
Cc: Venugopal, Rajesh
Subject: NDA 208558 - olaparib information request

Dear Ms. McCullough,

I am covering for RPM, Rajesh today. We have the following clinical information request:

You should submit the Case Report Forms for the following patients from SOLO2 for our review:
D0816C00002/E2301501

D0816C00002/E2307502

D0816C00002/E4304515

D0816C00002/E4304516

D0816C00002/E5003502

D0816C00002/E7001510

D0816C00002/E7001511

Please respond to this IR by tomorrow May 18, 2017 noon by email to facilitate review and by official submission to your NDA.

Thank you,

Janice

Janice Kim, PharmD, MS
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: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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/s/

JANICE H KIM
05/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Karen McCullough
U.S. Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. McCullough:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lynparza™ (olaparib) Tablet 100mg, 150mg.

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 Product:

1. Provide stability updates for all batches reported in section 3.2.P.8 as soon as they become available.
2. The analytical method for uniformity of dosage units notes that either (b) (4) or content uniformity by LC will be used. Because the film coated tablet results in a drug load (b) (4)%, the content uniformity by LC is more appropriate, as per USP <905>. Remove the option for (b) (4) to determine uniformity of dosage units in the drug product specification.
3. Regarding the enhanced analytical method approach described in section 3.2.P.5.1, FDA has the following comments. The approach is generally reasonable, but some changes are necessary to address post-approval concerns that may arise from the proposal.
    a. In addition to the exemplified system suitability requirements, (b) (4) for the HPLC columns or re-evaluation of linearity and range.
    b. Due to the gradient nature of the HPLC method, some modifications without revalidation are limited as per the USP<621>. When there are changes outside of the validated ranges (b) (4) (b) (4)

[redacted] (b) (4) confirm these changes will be reported FDA as a supplement including revalidation data.

c. To avoid differences between documentation on-site and within the current application on file, FDA recommends that changes to non-established conditions ("do and record") for the manufacturing process, control strategy, and analytical methods be reported by annual report. In addition to the 2004 "Guidance for Industry – Changes to an Approved NDA or ANDA" referenced in the meeting package, FDA also recommends consulting the 2014 "Guidance for Industry – CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports", which can be found at:
https://www.fda.gov/downloads/Drugs/.../Guidances/UCM217043.pdf

4. [redacted] (b) (4) will be denied.

5. [redacted] (b) (4) will be denied.

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 June 1, 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: 2017.05.12 15:40:45 -04'00'

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

From: Venugopal, Rajesh
To: "McCullough, Karen"
Cc: Chlysta, Lori A
Subject: RE: timing of mega-pk and question about GCP inspection
Date: Thursday, May 11, 2017 12:50:30 PM
Attachments: image001.png

Hi Karen,

Our clinpharm team wants to make sure that you will revise the draft labeling by including the information on (1) the relative bioavailability results of tablet and capsule and (2) PK parameters (AUC and Cmax) of 300 mg tablet after single and multiple dosing by June 1st?

In their email sent on May 5, 2017 below, you only stated updates of relative bioavailability info (highlighted in yellow) . So we would like to make sure AZ will include both info in the updated labeling according to our IR conveyed on May 2, 2017. Please confirm.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
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rajesh.venugopal@fda.hhs.gov

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Friday, May 05, 2017 10:50 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: timing of mega-pk and question about GCP inspection

Hi Rajesh,

First, I can confirm that we will deliver the mega-PK dataset and revised draft tablet USPI (updated with post-marketing hypersensitivity findings and relative bioavailability information) by June 1. It looks at the moment like it would go through the gateway on June 1, I can email those components that can be sent via email a day in advance.

I also wanted to touch base with you about timing of BIMO inspections. The GMP inspection is scheduled for 15-24 May. Inspection of two US SOLO2 sites concluded last week and went well (no

483s). The remaining inspections are scheduled as follows:

Week of June 12: Dr Pautier (France)
Week of June 19: Dr. Harter (Germany)
Week of July 3: sponsor inspection (Poland)

To allow time address any inspection findings and to generally keep inspections off the critical path, would it possible to move the sponsor inspection up? If you agree and would like to consider earlier dates, we would be happy to discuss it further with you. Holding the sponsor inspection during the week June 19 or the week of June 26 could be good options, given that the inspector will already in be Europe.

Best,
Karen

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RAJESH VENUGOPAL
05/11/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc: Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject: NDA 208558 (olaparib) - Clinical/Stats Information Request
Date: Monday, May 08, 2017 10:53:52 AM
Attachments: image001.png

Hello Karen,

The following comments/request comes from our clinical and statistics group. We ask that you respond by no later than 10 am Friday 5/12.

-

Clinical/ statistical IR RE: BIRC Assessments in SOLO2

-

1. Your responses to the IRs we have sent regarding BICR and datasets are not acceptable. We remind you what we communicated to you on 3/3/16 (via email), when you informed us of the change in your primary endpoint analysis from BICR to investigator assessment. We stated: "The Agency does not have any objections to changing the primary endpoint to investigator assessed PFS, provided that you conduct an independent central review of **all patient scans** to confirm the investigator assessment. Both PFS analyses assessed by investigator and central review should be consistent".

To date, we are unable to verify your primary PFS analysis by BICR assessment with the datasets you have provided. This is resulting in delay of our review and is raising questions surrounding the accuracy of the PFS results.

In order for us to conduct our analysis of efficacy you will need to explain the issues described below, and provide amended datasets as requested. The following table is our analysis, depicting the missing IRC data, in the form of censoring, as compared to the INV assessed events.

	Investigator Event			Investigator CNSR		
	Olaparib 300	Placebo bd	Total	Olaparib 300	Placebo bd	Total
IRC Event	80	66	146	1	4	5
IRC CNSR	27	14	41	88	15	103
	107	80	187	89	19	108

A total of 41(approximately 14%) of patients had an investigator assessed event but were censored according IRC assessment, 27 patients on the Olaparib arm and 14 patients on the placebo arm. Clarify how many of these patients:

1) Were censored because IRC assessments were not performed,
2) Had scans assessed by IRC but were assessed as censored, in these cases you should provide the reasons why these patients were censored by the IRC.

For the above you should also identify any patients where neither (1) nor (2) apply. Provide a

patient level listing.

-

Missing Data

Data set ADTR (Tumor results analysis for investigator assessment) has only data for 108 patients. You will need to resubmit this dataset with the tumor results for investigator assessments for all 295 patients, each patient having records for the following attributes in PARAM:

1	Absolute change from previous minimum sum of adjusted diameters excluding interventions (mm) including scaling
2	Absolute change from previous minimum sum of adjusted diameters including interventions (mm) including scaling
3	Adjusted Diameter (mm)
4	Number of lesions with diameters present at visit
5	Number of lesions without intervention with diameters present at visit
6	Percentage change from baseline sum of adjusted diameters excluding interventions (mm) including scaling
7	Percentage change from baseline sum of adjusted diameters including interventions (mm) including scaling
8	Percentage change from previous minimum sum of adjusted diameters excluding interventions (mm) including scaling
9	Percentage change from previous minimum sum of adjusted diameters including interventions (mm) including scaling
10	Previous minimum sum of adjusted diameters (mm) where all lesions are present
11	Previous minimum sum of adjusted diameters excluding interventions (mm) including scaling
12	Sum of adjusted diameters (mm)
13	Sum of adjusted diameters at previous minimum excluding lesions missing at the visit
14	Sum of adjusted diameters at previous minimum excluding lesions missing or with intervention at the visit
15	Sum of adjusted diameters excluding interventions (mm)
16	Sum of adjusted diameters excluding interventions (mm) including scaling, if appropriate
17	Sum of adjusted diameters including interventions (mm) including scaling, if appropriate

The corresponding measurement value for the above attribute should be in (AVAL/AVALC). If any of the attributes are missing, you should include an additional column giving the reasons why the attribute is missing. Do not exclude any of the columns currently in ADTR, and populate these columns with the information corresponding to the record.

-

Dataset RSTR

You should also resubmit dataset RSTR, where for each patient and each TREVAL(INVESTIGATOR) has all the following tumor attributes in PARAM:

PARAM
Actual Change From Baseline
Actual Change From Nadir

Any Non-target Lesion
Any Target Lesions Present
Longest Diameter
Percent Change From Baseline
Percent Change From Nadir
Short Axis
Sum of Diameter
Tumor State

This dataset should have corresponding measurement values for the tumor attributes in (AVAL/AVALC). If any of the attributes are missing, you should include an additional column giving reasons why the attribute is missing. Do not exclude any of the columns currently in ADTR and populate these columns with the information relevant to the record. You should also specify a method of linking dataset RSTR with dataset ADTR.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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/s/

RAJESH VENUGOPAL
05/08/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - Clinical Information Request
Date:	Friday, May 05, 2017 4:20:47 PM
Attachments:	image001.png

Hi Karen,

Information Request form our clinical team:

We are attempting to isolate the 90 patients with ovarian, fallopian tube, primary peritoneal cancers treated with 3 or more prior lines of anticancer therapy in the integrated AE dataset submitted 2/22/17. The specific analysis dataset is the ISS Tablet ADAE analysis dataset. Provide us with the appropriate flags to use in the dataset to isolate these 90 patients to conduct an AE analysis. (For reference, you identified these patients as being from studies 24, 4, 6, 7, 8 and 1 in your response to our April 13 Clin Pharm IR.)

Please respond by 3 PM Monday May 8, if not before.

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
05/05/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request
Date: Thursday, May 04, 2017 11:28:01 AM
Attachments: image001.png

Karen,

Our ClinPharm group is OK with your proposed assay to address 4.II 1), 4.II 2), and 4.III as you raised in the response to the 0413 Clin Pharm IR. To perform the proposed analysis, youdo not have to rely on the meta-PPK model. However, currently we are not exempting your group from performing the mega-PPK. But you may address 3b using the modeling deliverables described in the response to the 0413 clin pharm IR, instead of mega-PPK dataset.
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Wednesday, May 03, 2017 2:57 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request

Hi Rajesh,

The team met this morning. They had concerns about providing the mega-pk dataset by June 1, but I will investigate further get back to you.

Also, our folks planned to address 3b using the modeling deliverables described in the response to the 0413 clin pharm IR, as opposed to using the mega-PK dataset for the response. If we used the mega-PK dataset, we couldn't deliver the response by 12 May, so we assume that the clin pharm reviewer will be ok with this.

Best,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Wednesday, May 03, 2017 12:16 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Cc: Chlysta, Lori A <lori.chlysta@astrazeneca.com>
Subject: RE: NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request

Hi Karen,

With regards to ClinPharm question #1, I've double checked with them and they have said that they do want AZ to update the section 12.3 Pharmacokinetics in the proposed tablet labeling by including the information on the relative bioavailability results of tablet and capsule and PK parameters (AUC and C_{max}) of 300 mg tablet after single and multiple dosing. I was hoping to provide you with all of our comments first before you added the updates to postmarketing observations concerning hypersensitivity. But since they want an updated label please go ahead and add the hypersensitivity stuff as well now.

Do you think you can send the updated label before June 1? If so, can you guestimate when? Also, have you had a chance to speak with your team re: if you will be able to provide the mega-PK dataset by June 1?

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Tuesday, May 02, 2017 2:17 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request

Hi Rajesh,

Confirming receipt and due dates are noted. Will get this to the team.

Regarding request #1, we had planned to hold off on updating the proposed tablet USPI until we got your first round of comments on the label. If we submit an updated USPI to you by May 12, presumably we should also add in updates to postmarketing observations concerning hypersensitivity? We are happy to take whatever approach you prefer, just want to be sure no one gets confused along the way.

Regarding #3a, I am not sure the mega-PK dataset can be created and analyzed in 30 days. I will discuss with the team and get back to you as soon as possible.

Best,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, May 02, 2017 1:22 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Cc: Chlysta, Lori A <lori.chlysta@astrazeneca.com>
Subject: NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request

Hi Karen,

Our clinical pharmacology team has the following information requests that requires your response:

1. Please update the section 12.3 Pharmacokinetics in the proposed tablet labeling by including the information on the relative bioavailability results of tablet and capsule and PK parameters (AUC and C_{max}) of 300 mg tablet after single and multiple dosing.

2. [redacted] (b) (4)

3. Reference is made to your olaparib MS-01, MS-02 and MS-03 in the NDA208558 submission for olaparib. Reference is also made to your response to FDA information request (4/25/2017).

   a) We understand the potential difficulty in developing the meta-PPK analysis as

mentioned by the applicant's response to FDA's IR (4/25/2017). The proposed analysis plan in the applicant response to the IR (4/25/2017) [4.II.1 and 4.II.2] is acceptable if the applicant could find adequate data for support this analysis. However, the mega-PPK analysis as described in the IR (4/25/2017) will still be required to provide consistent PK parameters and model structures in terms of distributions and eliminations for both capsule and tablet by incorporating all available data. Especially, the time-dependent apparent clearance was not detected in the MS-01 for capsule formulation but detected at the tablet formulation (MS-02 and MS-03), this discrepancy should not be expected between this two formulations. A consistent PPK description on the drug distribution and elimination between these two formulations is expected by sharing one set of relevant PK parameters.

b) In addition, please conduct the exposure response analysis for safety, especially myelosuppresive adverse events at 4th line treatment setting in ovarian cancer patients with gBRCA mutation. Based on this model, provide prediction of safety profile at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in 4th line treatment setting in ovarian cancer patients with gBRCA mutation.

Please provide the written response with relevant datasets and programs to the item 3b) by COB of May 12th, 2017, and to the rest of the items by COB of June 1st, 2017.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
05/04/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (Oalaprib) - Clinical Pharmacology Information Request
Date:	Tuesday, May 02, 2017 1:21:40 PM
Attachments:	image001.png

Hi Karen,

Our clinical pharmacology team has the following information requests that requires your response:

1. Please update the section 12.3 Pharmacokinetics in the proposed tablet labeling by including the information on the relative bioavailability results of tablet and capsule and PK parameters (AUC and C_{max}) of 300 mg tablet after single and multiple dosing.

2. (b) (4)

3. Reference is made to your olaparib MS-01, MS-02 and MS-03 in the NDA208558 submission for olaparib. Reference is also made to your response to FDA information request (4/25/2017).

   a) We understand the potential difficulty in developing the meta-PPK analysis as mentioned by the applicant's response to FDA's IR (4/25/2017). The proposed analysis plan in the applicant response to the IR (4/25/2017) [4.II.1 and 4.II.2] is acceptable if the applicant could find adequate data for support this analysis. However, the mega-PPK analysis as described in the IR (4/25/2017) will still be required to provide consistent PK parameters and model structures in terms of distributions and eliminations for both capsule and tablet by incorporating all available data. Especially, the time-dependent apparent clearance was not detected in the MS-01 for capsule formulation but detected at the tablet formulation (MS-02 and MS-03), this discrepancy should not be expected between this two formulations. A consistent PPK description on the drug distribution and elimination between these two

formulations is expected by sharing one set of relevant PK parameters.

b) In addition, please conduct the exposure response analysis for safety, especially myelosuppresive adverse events at 4th line treatment setting in ovarian cancer patients with gBRCA mutation. Based on this model, provide prediction of safety profile at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in 4th line treatment setting in ovarian cancer patients with gBRCA mutation.

Please provide the written response with relevant datasets and programs to the item 3b) by COB of May 12th, 2017, and to the rest of the items by COB of June 1st, 2017.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
05/02/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc: Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject: NDA 208558 (olaparib) - Clinical Information Request
Date: Friday, April 28, 2017 9:25:17 AM
Attachments: image001.png

Hi Karen,

Below is a clinical information request that requires your response. Please respond by 10 AM Wednesday May 3. Thank you.

1) In 2.7.4, it states that there have been 32 reports of MDS/AML out of a total of 6558 patient exposed to olaparib as of 12/15/16. You should provide the following information on all 32 reports. We note that when accounting for cases in patient exposed to olaparib in all studies, we have calculated 27 cases in patients with any exposure to olaparib, and excludes patients randomized to placebo on randomized trials if they were never exposed to olaparib at any time (even after randomized therapy with placebo). In order to avoid confusion and to facilitate a timely response, we are providing the patient ID numbers and study numbers that we have already counted.

#	Study	Patient ID/ Age	Arm
1	19	E1801002 77y	Olaparib
2	19	E0801001 53 y	Olaparib
3*	19	E1808004 49 y/o	olaparib
4	41	E1405004 78y	Olaparib + carbo/ taxol→ olaparib
5	41	E1503001 61y	Olaparib + carbo/ taxol→ olaparib
6	12	E7001010 71y	olaparib
7	12	E6007014 63 y	olaparib
8	42	E0302009 63y	olaparib
9	42	E4007006 63y	olaparib
10	42	E4003003 45y	olaparib

11	42	E7802003 55y	olaparib
12	42	E7802029 61 y	olaparib
13	42	E4001012 51 y	olaparib
14	9	E0017011 68 y	olaparib
15	9	E0613008 63 y	olaparib
16	2	001-0078 70 y	olaparib
17	4	003-2117 64 y	olaparib+ C/P
18	98	E8348038 67 y	olaparib + cediranib
19	59	0810C00059/008 60 y	Olaparib+ carboplatin + paclitaxel
20	24	E0008004 50 y/o female	Olaparib 400 mg bid
21	INV (55)	D0810C0055/JH001 67 y/o male	Olaparib 100 bid intermit-tent (w/ irino/cis/mito-C)
22	INV (55)	D0810C0055/JH004 67 y/o male	Olaparib 100 mg bid intermittent (w/ irino/cis)
23	SOLO2	E2804503 56 y/o female	Olaparib 300 mg BID tablet
24	SOLO2	E7001507 71 y/o female	Olaparib 300 mg BID tablet
25	SOLO2	E2309503 42 y/o female	Olaparib 300 mg BID tablet
26	SOLO2	E2601508 53 y/o female	Olaparib 300 mg BID tablet
27	SOLO2	E2307506 44 y/o female	Placebo→ Olaparib open-label after PD on placebo

When providing the additional cases for us, you should include: Study number, patient ID number, patient age, BRCA status, underlying tumor, olaparib formulation (tablet vs. capsule) and dose, number of days exposed to olaparib, diagnosis (MDS vs. AML vs. other hematologic malignancy, such as CMML), cytogenetics if reported, whether the event resulted in death (or patient died, even if attribution was considered due to another cause) or if the event was ongoing. You should provide narratives for any of these 32 patients that have not yet been provided in a document that is easy to navigate, by patient ID/ study number. Shown below is an example of the complete tabular format requested (from a patient diagnosed with MDS on Study 19), in addition to the narratives.

#	Stu-dy	Patient ID/ Age	Arm/ Forumlation and dose	Cancer under treatment	BRCA stat.	Days on study drug	diagnosis	Cytogenetics	outcome
1	19	E1801002 77y	Olaparib/ Capsule 400 mg BID	Primary peritoneal	gBRCA wild	313	MDS- RAEB	5q-, 17p-, abn 7q	death

2) A point of clarification is requested, as well. In 2.7.4 Summary of Clinical safety, the report that there were 2 cases of MDS/AML on study 24. There previously was only 1 case identified from this study (patient ID E0008004). Provide patient ID for the other case on Study 24, as well as narrative with details of the case.

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

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RAJESH VENUGOPAL
04/28/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, April 13, 2017 5:48 PM
To: 'Karen.McCullough@astrazeneca.com'
Cc: lori.chlysta@astrazeneca.com; Venugopal, Rajesh
Subject: NDA 208558; Olaparib--Additional Clinical/Statistical Information Request

Importance: High

Dear Karen:

Relative to AZ's NDA for Olaparib, the clinical/statistical reviewers have the following request for information:

CLINICAL/STATISTICAL REQUEST FOR INFORMATION: IRC ASSESSMENT OF SCANS:

1. We want to further clarify the role of the BICR in scan assessment through the course of the SOLO2 study. Did all patients have baseline scans sent for BICR assessment, or were scans only sent to the BICR after baseline, when the investigator determined there was disease progression? In the most recent dataset sent (XX BICR/ INV dataset), there are missing assessments, mainly for the BICR assessments, but it is unclear if the missing observations are due to the BICR not reviewing these particular scans, or because there were no evaluable lesions according to BICR (and therefore no entry was put into the dataset). Provide a dataset (or amend RSTR,RSRS or XX BICR/INV dataset s) that includes patient ID number, treatment arm, dates of scan and a flag for each scan's date to indicate whether the scans for that date (for each scan a patient had while on study) were IRC reviewed. We are trying to determine the date for each patient **when scans were no longer sent for IRC review.**

Please provide a response to this query by **4:00pm EST, Monday, April 17, 2017**.

Regards,
Kim for Rajesh

Kim J. Robertson
Regulatory Health Project Manager

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kim.robertson@fda.hhs.gov

Reference ID: 4084183

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KIM J ROBERTSON
04/13/2017

Robertson, Kim

From:	Robertson, Kim
Sent:	Thursday, April 13, 2017 5:44 PM
To:	'Karen.McCullough@astrazeneca.com'
Cc:	'lori.chlysta@astrazeneca.com'; Venugopal, Rajesh
Subject:	NDA 208558 (Olaparib)--Clinical/Clinical Pharmacology Information Request
Importance:	High

Dear Karen:

I am covering my colleague Rajesh today, while he is away on leave. Relative to AZ's NDA (208558) for Olaparib, please see the following requests for information:

Clinical/ Clinical Pharmacology Request for Information:

1. Since it has been determined that the tablet and capsule formulations of olaparib are not bioequivalent, we are trying to assess whether there is clinical data available to support the safety and efficacy of the tablet formulation and dose (300 mg BID) in the currently approved setting (monotherapy for ovarian cancer patients who have received 3 or more prior lines of therapy). We acknowledge that there is data described in the "Tablet Pool", but we are trying to quantify the amount of more specific safety and efficacy data to support the already approved ovarian cancer indication. Please provide a summary of the number of patients who may be applicable to this indication, including which study they were treated on, and dose and duration of treatment with the tablet formulation.

2. Please provide your analyses for exploring why the exposure to olaparib in study SOLO2 is lower than that in the pooled tablet PK analysis (300 mg BID). Please submit the data and analysis method for the investigation you conducted using the factors listed in slide 31 of your AOM presentation.

3. Please provide your opinion on whether a PK matching method can be used to identify the appropriate tablet dose for the fourth line treatment indication.

4. Reference is made to your MS-01, MS-02 and MS-03 in the NDA208558 submission for olaparib.

I. Submit the datasets and control stream for the PPK and E-R analysis in MS-03.

II. Combine all available PK data from different patient populations and healthy subjects in your integrated population PK model to evaluate the impact of formulations, treatment lines, disease severity, tumor types or other relevant factors on the PK of olaparib:

   a. Data for PPK analysis of MS-01, MS-02 and MS-03 should all be included.
   b. If necessary, the absorption process could be described by distinct functions based on the formulations (capsule vs. tablet).
   c. The drug distribution and elimination of capsule and tablet should be described by the same set of functions
   d. Estimate the relative bioavailability for tablet as compared with capsule; if the extent of drug absorption is dose dependent with capsule formulation, take dose<100 mg, fast/unknown release capsule as the reference.

Reference ID: 4084182

e. Assess if the treatment line, disease severity, tumor types, or other factors may potentially impact the olaparib PK profile by evaluating them as covariates.

Please use this mega-PPK analysis to:

1) Evaluate the exposure profile changes (Cmax, Cmin, AUCss, etc.) at the treatment group (4th line ovarian cancer patients) by switching from the 400 mg capsule into 300 mg tablet formulation. In addition, please also compare the exposure profiles at the treatment group for the secondary dose levels (200 mg capsule vs. 250 mg tablet, 100 mg capsule vs. 200 mg tablet). This comparison will be simulation based.
2) Evaluate the reason that the exposure at SOLO2 study was lower as compared with the tablet pooled population.

III. Conduct the exposure response analysis for safety, especially myelosuppresive adverse events at 2nd + line treatment setting in ovarian cancer patients with gBRCA mutation. Predict and compare the safety profile following 300 mg tablet BID and 400 mg capsule BID in these 2nd + line treatment setting in ovarian cancer patients. In addition, provide prediction of safety profile at exposure level 50%, 70% and 100% higher than 400 mg BID capsule in 2nd + line treatment setting in ovarian cancer patients with gBRCA mutation.

For the item **4(I)**, please respond by **4:00pm EST Monday, April 17, 2017**. For the remaining items, please provide responses with relevant datasets and programs to the corresponding items by **4:00pm EST Tuesday, April 25, 2017**.

Regards,
Kim for Rajesh

Kim J. Robertson
Regulatory Health Project Manager

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KIM J ROBERTSON
04/13/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - Followup IR for request for dataset combining Investigator and BICR assessments.
Date:	Friday, April 07, 2017 6:51:10 AM
Attachments:	image001.png

Hi Karen,

We request that you provide the previously requested dataset, which provides individual lesion measurements **(unadjusted)** by both IRC and INV assessment at each visit in ONE dataset. Also include Overall Response assessment (CR, PR, SD, PD, etc) by IRC and INV for each visit within this same dataset.

We acknowledge your request for an additional 48 hours to provide this dataset. This timeframe to provide the dataset is acceptable.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
04/07/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Cc:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject:	NDA 208558 (olaparib) - Clinical Stats Information Request
Date:	Tuesday, April 04, 2017 12:42:58 PM
Attachments:	image001.png

Hello Karen,

The clinical and stats team are trying to do an analysis of tumor responses by investigator and BIRC assessment, including assessment of individual lesions. They note that the RSTR dataset does not have actual investigator measurements for lesions, and the ADTR file contains investigator measures, but these are listed as "adjusted" measurements. Please submit a dataset that provides individual lesion measurements by both IRC and INV assessment at each visit in ONE dataset. It would also be helpful to include Overall Response assessment (CR, PR, SD, PD, etc) by IRC and INV for each visit within this same dataset. Please also provide details into the method for how the "adjusted measurements" were computed (in the original ADTR dataset), and if possible, provide the data for "unadjusted" measurements for our analysis.

Please provide the information requested by 2 PM Thursday April 6.

Regards,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
04/04/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject: NDA 208558 (Olaparib) - OSI Information Request
Date: Wednesday, March 29, 2017 9:45:54 AM
Attachments: image001.png
image002.png

Hi Karen,

Our Office of Scientific Investigations review team has the following information request requiring your response:

For each clinical site for **study D0816C00002** provide the information in PDF bookmarked file structure provided below.

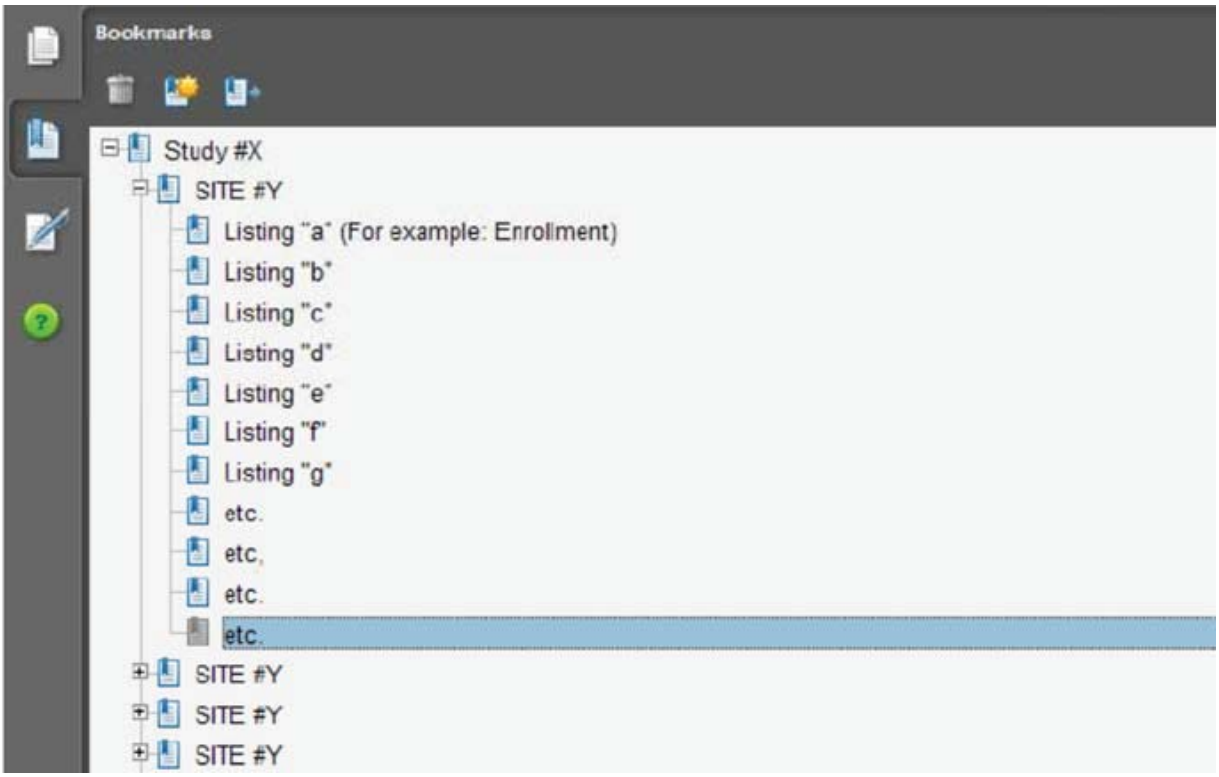
Study D0816C00002 Data listings
- Site 1
  - Listing a
    - Subject 001
    - Subject 002 ect
  - Listing b
  - Listing c
  - For all requested listings
- Site 2, and so on for all sites

What you have provided has the information we previously requested, but in a format that is not conducive to clinical site inspections and data validation. You should submit a PDF with bookmarks for each clinical site, then book marked for each datalisting parameter, each DL presented by subject. See below.

II. Request for Subject Level Data Listings by Site

1. For **Study D0816C00002)** : 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 351(k) BLA, 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 clinical studies)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring.

2. We request that one PDF file be created for **Study D0816C00002** using the following format:



Please respond by 3 PM Friday March 31, 2017.

Thanks ,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
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rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
03/29/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject: NDA 208558 (olaparib) Clinical Pharmacology Information Request
Date: Wednesday, March 29, 2017 9:25:09 AM
Attachments: image001.png

Hello Karen,

Our Clinical Pharmacology team has the following information request that requires your response:

1. In your report, you indicated that you used an earlier raltegravir model (Hartmann et al). Provide details on model development and verification for raltegravir as a UGT1A1 substrate for the purpose of predicting UGT1A1 inhibition by an investigational drug.
2. Provide model files used to generate final PBPK simulations in the PBPK reports (e.g. drug model files, population files, and workspace files, .cmpz, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Please respond by 3PM Thursday April 6, 2017.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
03/29/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Subject: RE: NDA 208558 (Olaparib) - Clinical/Stats Information Request
Date: Tuesday, March 28, 2017 10:51:50 AM
Attachments: image001.png
IR Table for protocol version and SAP version enrollment.docx

---

Hi Karen,

Upon review of the submission, the clinical team asks that you fill in/correct the 2 tables with enrollment numbers and dates for the SOLO2 trial in the attached form and send back to me by 5 PM today, if not sooner.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
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rajesh.venugopal@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Monday, March 27, 2017 2:52 PM
To: Venugopal, Rajesh
Subject: RE: NDA 208558 (Olaparib) - Clinical/Stats Information Request

Hi Rajesh – the submission has gone through the gateway. Since it is large, I don't think I can attach to an email.

Best,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, March 27, 2017 12:46 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: RE: NDA 208558 (Olaparib) - Clinical/Stats Information Request

No worries Karen. Understood. I'll let the review team to expect it later today.

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]

Sent: Monday, March 27, 2017 12:41 PM
To: Venugopal, Rajesh
Subject: RE: NDA 208558 (Olaparib) - Clinical/Stats Information Request

Hi Rajesh,

The response is complete, but we are in the process of publishing it. That is a time consuming process and it is taking longer than expected, but I hope to have it within the hour.

Apologies for the delay.

Best,
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, March 21, 2017 3:02 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (Olaparib) - Clinical/Stats Information Request

Hi Karen,

We have the following clinical/Stats information request requiring a response:

1. Please provide all case report forms for patients who died during study or within 30 days of discontinuation, patients who experienced a serious adverse event on study, and for all patients who discontinued therapy due to an adverse event. You should also provide case report forms for the 8 patients who were diagnosed with MDS/AML at any point during or after therapy.

2. Please provide the patient narratives with hyperlinks to individual narratives in the table of contents. The current format of the narratives in Section 11 of the CSR does not allow any mechanism to navigate to individual narratives from the table of contents.

3. There appear to have been 8 patients on SOLO2 diagnosed with MDS/AML, but narratives for only 7 of them appear to have been provided. Provide narratives for all 8 cases of MDS/AML. These narratives should include information on all prior therapies for the underlying ovarian cancer, and the dates of these therapies, as well as information of time course of cytopenias that may have led to suspicion and assessment for MDS/AML by bone marrow analysis. Information on results of bone marrow analysis and cytogenetics should be included, as well as any long- term follow up information, including therapy received for MDS/AML and whether patient was still alive at the time of data cut off.

4. You should provide final versions of the protocol after Amendment #2 and Amendment#3. Please provide the tracked changes versions of these documents as compared to the original protocol. Provide the date of implementation of each amendment at the beginning of the

document, as well as study enrollment information at the time of the implementation.

5. Provide all versions (amendments) of the Statistical Analysis Plan, shown as tracked changes when compared to the original SAP. Provide the date of implementation of each version, as well as study enrollment at the time of implementation.

Please respond by 12 PM Monday, March 27, 2017.

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

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Please fill in the tables below, and correct any errors (with tracked changes) if applicable:

Protocol version	**Effective date**	**Enrollment**	
		Screened	**Randomized**
Original	4/24/13		
Amendment 1	12/4/13		
Amendment 2	9/15/14	481	197
Amendment 3	4/12/16	603	295

SAP version	**Effective date**	**Enrollment**	
		Screened	**Randomized**
Original (?Edition 1)	12/18/13	35	8
SAP Edition 2	1/12/16	-	295 (complete)
SAP Edition 3	4/22/16	-	295 (complete)

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/s/

RAJESH VENUGOPAL
03/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Karen McCullough
U.S. Regulatory Affairs Director, Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. McCullough:

Please refer to your New Drug Application (NDA) dated and received February 27, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lynparza™ (olaparib) Tablet 100mg, 150mg.

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 Product:

1. Section 3.2.P.4.1 states that "the film coats may be supplied as a proprietary concentration" Provide a letter of authorization for the DMF of any proprietary film coat or revise section 3.2.P.4.1 to state that only in-house tablet coat mixtures will be used in the manufacturing process.

2. Section 3.2.P.8.3 reports the results of (b) (4) stability studies. These results show (b) (4)

Please respond to Drug Product comments by COB April 3, 2017.

Biopharmaceutics:

1. [redacted]

2. Please note that for poorly soluble drugs and slowly dissolving drug products, the selection of 2 time points for the setting of the dissolution acceptance criteria is appropriate. Based on the dissolution data provided, we recommend that you implement the following dissolution acceptance criteria for olaparib 150 mg tablets and provide the revised specifications table with the updated acceptance criterion for the dissolution test:

   NLT [redacted]% in 30 min
   Q=[redacted]% in 60 min

Please respond to Biopharmaceutics comments by COB April 3, 2017.

Drug Process:

1. [redacted]
2.
3.
4.
5.
6.

7. (b) (4)

8.

9.

10.

11.

Please respond to Drug Process comments by COB April 21, 2107

If you have any questions, please contact me, Kristine Leahy, RPh., Regulatory Business Process Manager, at (240) 402-5834.

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: 2017.03.24 14:26:49 -04'00'

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

AstraZeneca Pharmaceuticals LP
Attention: Karen McCullough, PhD
Director, Global Regulatory Affairs Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. McCullough:

Please refer to your New Drug Application (NDA) dated February 22, 2017, received February 22, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Lynparza™ (olaparib) Tablets, 100 mg and 150 mg.

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 August 22, 2017.

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 post-marketing requirement/commitment requests by August 1, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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.

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 Medication Guide. 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 Medication Guide, 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

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JULIA A BEAVER
03/24/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 208558 (Olaparib) - CLinical Information Request
Date:	Thursday, March 23, 2017 5:35:42 PM
Attachments:	image001.png

One last thing to the IR below:

Please provide a detailed define file for SOLO2 with similar level of detail as that in Trial 19.

rajesh
Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Thursday, March 23, 2017 5:34 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Olaparib) - CLinical Information Request

Confirming receipt, Rajesh.

We'll get back to you ASAP.
Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, March 23, 2017 5:21 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (Olaparib) - CLinical Information Request

HI Karen,

Please see the following clinical information request requiring a response:

We are unable to derive the analysis on baseline disease characteristics shown in Table 13 of the CSR for SOLO2, including primary tumor location, tumor grade, histology, disease classification at

study entry, prior cytoreductive surgery, and time from last platinum (< 8 wk vs. > 8 wks). Provide us with an analysis dataset to perform this analysis, or direct us to the location of this dataset in the NDA submission. Provide a response by 1pm Friday 3/24.

Please respond by 1 PM tomorrow Friday March 24.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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U.S. Food and Drug Administration
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rajesh.venugopal@fda.hhs.gov

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RAJESH VENUGOPAL
03/23/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - CLinical Information Request
Date:	Thursday, March 23, 2017 5:20:50 PM
Attachments:	image001.png

HI Karen,

Please see the following clinical information request requiring a response:

We are unable to derive the analysis on baseline disease characteristics shown in Table 13 of the CSR for SOLO2, including primary tumor location, tumor grade, histology, disease classification at study entry, prior cytoreductive surgery, and time from last platinum (< 8 wk vs. > 8 wks). Provide us with an analysis dataset to perform this analysis, or direct us to the location of this dataset in the NDA submission. Provide a response by 1pm Friday 3/24.

Please respond by 1 PM tomorrow Friday March 24.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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RAJESH VENUGOPAL
03/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

PROPRIETARY NAME ACKNOWLEDGEMENT

AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Karen McCullough, PhD
Director, Global Regulatory Affairs Oncology

Dear Dr. McCullough:

Please refer to your New Drug Application (NDA) dated and received February 22, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olaparib Tablets, 100 mg and 150 mg.

We acknowledge receipt of your correspondence dated and received February 27, 2017, requesting a review of your proposed proprietary name, Lynparza.

If the application is filed, the user fee goal date for your proposed proprietary name will be May 28, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-0942. For any other information regarding this application, contact Rajesh Venugopal, Regulatory Project Manager, in the Office of New Drugs at (301)796-4730.

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
03/22/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - Clinical/Stats Information Request
Date:	Tuesday, March 21, 2017 3:01:52 PM
Attachments:	image001.png

Hi Karen,

We have the following clinical/Stats information request requiring a response:

1. Please provide all case report forms for patients who died during study or within 30 days of discontinuation, patients who experienced a serious adverse event on study, and for all patients who discontinued therapy due to an adverse event. You should also provide case report forms for the 8 patients who were diagnosed with MDS/AML at any point during or after therapy.

2. Please provide the patient narratives with hyperlinks to individual narratives in the table of contents. The current format of the narratives in Section 11 of the CSR does not allow any mechanism to navigate to individual narratives from the table of contents.

3. There appear to have been 8 patients on SOLO2 diagnosed with MDS/AML, but narratives for only 7 of them appear to have been provided. Provide narratives for all 8 cases of MDS/AML. These narratives should include information on all prior therapies for the underlying ovarian cancer, and the dates of these therapies, as well as information of time course of cytopenias that may have led to suspicion and assessment for MDS/AML by bone marrow analysis. Information on results of bone marrow analysis and cytogenetics should be included, as well as any long- term follow up information, including therapy received for MDS/AML and whether patient was still alive at the time of data cut off.

4. You should provide final versions of the protocol after Amendment #2 and Amendment#3. Please provide the tracked changes versions of these documents as compared to the original protocol. Provide the date of implementation of each amendment at the beginning of the document, as well as study enrollment information at the time of the implementation.

5. Provide all versions (amendments) of the Statistical Analysis Plan, shown as tracked changes when compared to the original SAP. Provide the date of implementation of each version, as well as study enrollment at the time of implementation.

Please respond by 12 PM Monday, March 27, 2017.

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845

rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
03/21/2017

From:	Venugopal, Rajesh
To:	"McCullough, Karen"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 208558 (Olaparib) - Clinical Information request
Date:	Tuesday, March 21, 2017 8:36:57 AM
Attachments:	image001.png image007.png

HI Karen,

We would like the **contact person name and phone number** for the location of the Trial Master Files at AZ in Warsaw Poland (as noted from your response to the IR). Could you please provide this information today?

Thank you, Rajesh.

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Monday, March 20, 2017 12:49 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (Olaparib) - Clinical Information request

Hi Rajesh,

Attached are our responses to the IR sent on 17 March. We will formally the response on Wednesday, March 22.

You will note that the response provides contact information for the CRO responsible for the BICR, but defers to prior responses for questions concerning the TMF and the radiology charter. I hope this answers the clinical reviewer's questions – please let me know if we have misunderstood what their request.

Best,

Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, March 17, 2017 1:27 PM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (Olaparib) - Clinical Information request

Hi Karen,

Our clinical group has another information request for you re: 208558:

Provide us with information on who conducted the Blinded Independent Central Review for the primary endpoint sensitivity analyses for SOLO-2 (agreed to in the correspondence from FDA on 3/3/16), including the name, address, phone number for this group/CRO, and the location of the trial master files they utilized to perform their assessments. Also, provide us with the Radiology Charter employed by the BICR in conducting their analyses, as well as any other Radiology Charters that may have been employed during conduct of the SOLO-2 study, if applicable.

Please respond by 3 PM Monday, March 20, 2017.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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
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/s/

RAJESH VENUGOPAL
03/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

PROPRIETARY NAME ACKNOWLEDGEMENT

AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Karen McCullough, PhD
Director, Global Regulatory Affairs Oncology

Dear Dr. McCullough:

Please refer to your New Drug Application (NDA) dated and received February 22, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olaparib Tablets, 100 mg and 150 mg.

We acknowledge receipt of your correspondence dated and received February 27, 2017, requesting a review of your proposed proprietary name, Lynparza.

If the application is filed, the user fee goal date for your proposed proprietary name will be May 28, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-0942. For any other information regarding this application, contact Rajesh Venugopal, Regulatory Project Manager, in the Office of New Drugs at (301)796-4730.

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
03/20/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject: NDA 208558 (Olaparib) - Clinical Information request
Date: Friday, March 17, 2017 1:27:03 PM
Attachments: image001.png

Hi Karen,

Our clinical group has another information request for you re: 208558:

Provide us with information on who conducted the Blinded Independent Central Review for the primary endpoint sensitivity analyses for SOLO-2 (agreed to in the correspondence from FDA on 3/3/16), including the name, address, phone number for this group/CRO, and the location of the trial master files they utilized to perform their assessments. Also, provide us with the Radiology Charter employed by the BICR in conducting their analyses, as well as any other Radiology Charters that may have been employed during conduct of the SOLO-2 study, if applicable.

Please respond by 3 PM Monday, March 20, 2017.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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/s/

RAJESH VENUGOPAL
03/17/2017

From: Venugopal, Rajesh
To: "McCullough, Karen"
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (olaparib) - Clinical Information Request
Date: Tuesday, March 14, 2017 6:36:59 AM
Attachments: image007.png
image013.png

Hi Karen,

Yes we intend to conduct bimo audits. Please identify a location where we may conduct an audit of Sponsor activities and oversight of key studies supporting NDA 208558 (primarily SOLO2).
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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: 301-796-4730
Fax: 301-796-9845
rajesh.venugopal@fda.hhs.gov

From: McCullough, Karen [mailto:Karen.McCullough@astrazeneca.com]
Sent: Monday, March 13, 2017 2:08 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 208558 (olaparib) - Clinical Information Request

Hi Rajesh – a quick follow up to question 2 below. Our TMF is maintained electronically – there is no physical site where hard copies of documents are maintained.

I presume that this question is related to BIMO activities. Is it sufficient to give an address where the e-records could be viewed?

Karen

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, March 13, 2017 10:30 AM
To: McCullough, Karen <Karen.McCullough@astrazeneca.com>
Subject: NDA 208558 (olaparib) - Clinical Information Request

Hi Karen,

Our clinical review team have the following information request that requires your response:

1. Provide us with the charter (and all amendments for the charter) that was utilized by the BIRC to conduct response analysis for the primary PFS endpoint. Provide a timeline for when the primary endpoint was changed to investigator-assessed PFS, including when the statistical analysis plan was changed to reflect the change in analysis of the primary endpoint. If a separate charter was used by investigators in assessment of PFS, provide that as well. Confirm how many patients had been enrolled to SOLO2 at the time of the change in primary endpoint analysis from BIRC to investigator-assessed.

2. Provide us with the physical location (address) of the trial master files for SOLO2.

Please respond by 3 PM Wednesday, March 15, if not sooner.
Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health 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
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rajesh.venugopal@fda.hhs.gov

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RAJESH VENUGOPAL
03/14/2017

From: Venugopal, Rajesh
To: McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject: NDA 208558 (olaparib) - Clinical Information Request
Date: Monday, March 13, 2017 10:30:12 AM
Attachments: image001.png

Hi Karen,

Our clinical review team have the following information request that requires your response:

1. Provide us with the charter (and all amendments for the charter) that was utilized by the BIRC to conduct response analysis for the primary PFS endpoint. Provide a timeline for when the primary endpoint was changed to investigator-assessed PFS, including when the statistical analysis plan was changed to reflect the change in analysis of the primary endpoint. If a separate charter was used by investigators in assessment of PFS, provide that as well. Confirm how many patients had been enrolled to SOLO2 at the time of the change in primary endpoint analysis from BIRC to investigator-assessed.

2. Provide us with the physical location (address) of the trial master files for SOLO2.

Please respond by 3 PM Wednesday, March 15, if not sooner.

Thank you,

rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
Office of Hematology and Oncology Products
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rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
03/13/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject:	NDA 208558 (Olaparib) - CLinical Pharmacology information Request
Date:	Thursday, March 09, 2017 10:22:20 AM
Attachments:	image001.png

Hello Karen,

Our clinical pharmacology review team has the following information request that requires you response:

Please provide a table to list the study reports in Modules 5.3.1, 5.3.2, 5.3.3, and 5.3.4 that were not submitted in the capsule NDA 206162 and its supplements.

Please provide your response by 3PM March 14, 2017, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
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/s/

RAJESH VENUGOPAL
03/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208558

NDA ACKNOWLEDGMENT

AstraZeneca Pharmaceuticals LP
Attention: Karen McCullough, PhD
Director, Global Regulatory Affairs Oncology
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. McCullough:

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: LYNPARZA™ (olaparib) Tablets/100 mg, 150 mg

Date of Application: February 22, 2017

Date of Receipt: February 22, 2017

Our Reference Number: NDA 208558

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 April 23, 2017, 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 (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior 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/

RAJESH VENUGOPAL
02/23/2017

From: Fahnbulleh, Frances
To: Karen.McCullough@astrazeneca.com
Cc: Venugopal, Rajesh
Subject: Rolling Submission NDA 208558 Olaparib Tablets-Proprietary Name Request

Date: Friday, February 03, 2017 4:14:41 PM

Dear Karen,

Reference is made to your Rolling submission for NDA 208558. It is our understanding that this application provides for olaparib tablets which is a new formulation from the approved capsules NDA 206162, with the Proprietary Name, Lynparza. Please note that since this is a new NDA, the Proprietary Name must also be submitted for review under this current NDA. Since the application has been granted Fast Track designation, it is important that you submit the request as soon as possible.

Please refer to the Guidance for details:

Contents of a Complete Submission for the Evaluation of Proprietary Names:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

Let me know if you have any questions.

Respectfully,

Frances Fahnbulleh

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#4404
Ph: 301-796-0942/Fax: 301-796-9832
Email: Frances.Fahnbulleh@fda.hhs.gov

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FRANCES G FAHNBULLEH
02/03/2017

From:	Venugopal, Rajesh
To:	McCullough, Karen (Karen.McCullough@astrazeneca.com)
Subject:	NDA 208558 - Rolling Submission Part 2 - Information Request
Date:	Monday, January 23, 2017 11:12:02 AM
Attachments:	image001.png

Hello Karen,

Our OSI Site Selection Tool Group has the following information request that requires your immediate response:

Regarding your 1/10/2017 submission to NDA 208558 containing a clinsite.xpt file, the data entered for both ENROLL and TRTEFFR variables are identical. Please confirm that all enrolled subjects experienced endpoint event (TRTEFFR), or if data reported in error, provide a corrected clinsite.xpt file.

Please respond as soon as soon as possible.

rajesh
Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager

Division of Oncology Products 1
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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rajesh.venugopal@fda.hhs.gov

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/s/

RAJESH VENUGOPAL
01/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075918

MEETING PRELIMINARY COMMENTS

AstraZeneca Pharmaceuticals LP
Attention: Karen McCullough, PhD
US Regulatory Affairs Director
1800 Concord Pike
Wilmington, DE 19803

Dear Dr. McCullough:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LYNPARZA™ (olaparib).

We also refer to your November 7, 2016, correspondence, received November 7, 2016, requesting a meeting to discuss your pivotal clinical trial results with the Agency.

Our preliminary responses to your meeting questions are enclosed.

You should provide me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Senior Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: IND 075918
Product Name: LYNPARZA™ (olaparib).
Indication: Lynparza™ is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy:

- For the maintenance treatment of patients with platinum-sensitive relapsed high grade epithelial ovarian cancer, who are in response (complete response or partial response) (b) (4) (b) (4) platinum-based chemotherapy.
- In patients with deleterious or suspected deleterious *gBRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 19, 2017, 11:00 AM – 12:00 PM, 10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903, between AstraZeneca Pharmaceuticals LP and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Olaparib, a PARP inhibitor, was granted accelerated approved on December 19, 2014, for the following indication using the capsule formulation: "Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an

FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy." The applicant is seeking regular marketing approval for the use of the tablet formulation of olaparib for the maintenance treatment of patients with platinum-sensitive relapsed (PSR) ovarian cancer regardless of gBRCA status. The purpose of the meeting is to share clinical trial results and obtain feedback on a planned NDA. The proposed application includes data from two trials:

SOLO2: Olaparib tablet 300 mg PO BID as maintenance treatment for women with BRCAm PSR ovarian cancer (completion of this study was a PMR for olaparib's accelerated approval); and

Study 19: Olaparib capsule 400 mg PO BID as maintenance treatment for women (with BRCA-unselected PSR ovarian cancer.

In both trials, women with PSR ovarian cancer who were in response to their penultimate platinum regimen and who had received at least two prior lines of platinum-based treatment were randomized to receive olaparib or placebo until disease progression, with primary endpoint of investigator-assessed PFS. Briefly, the topline results demonstrate:

SOLO2: Median PFS 19.1m for olaparib (n=195) vs 5.5 for placebo (n=99), HR 0.30 (95%CI: 0.22 - 0.41); OS data are immature. No new safety signals were identified.

Study 19: Median PFS of 8.4m (n=136) vs 4.8m (n=129), HR 0.35 (95%CI: 0.25 - 0.49); OS 29.8m vs 27.8m (HR 0.73; 95%CI: 0.55-0.95); no new safety signals identified.

DISCUSSION

1. *Based on the totality of the data presented, does the Agency agree that the results of the olaparib pivotal studies in the PSR maintenance setting support submission of an NDA in the proposed indication?*

FDA Response:

Yes.

2. *Based on the clinical evidence (safety/efficacy) generated from SOLO2 and the risk:benefit profile of olaparib, does the Agency agree these results have the potential to fulfill PMR 2824-1 and thereby convert olaparib capsule approval status from 'Accelerated' to 'Full'?*

FDA Response:

Yes.

3. *When olaparib capsules received Accelerated Approval in December 2014, two PMRs were related to conversion to full approval: PMR2824-1 (related to SOLO2) and 2824-2 (related to D0816C00010, known as SOLO3). Does the Agency agree that if the proposed NDA is approved, SOLO3 is no longer needed to fulfill Subpart H requirements?*

FDA Response:

Yes; however, the Agency affirms that SOLO3 represents a critical trial and would provide valuable information regarding the utility of olaparib in the 3rd-line setting. Patients who elect against maintenance treatment, or who are ineligible for maintenance treatment, will gain answers to an important question with the results of this trial. The Agency recommends that the Sponsor continue SOLO3 until completion.

4. *On the basis of SOLO2 and Study 19 results, AstraZeneca intends to request priority review. Does the Agency agree that this is an acceptable approach?*

FDA Response:

Yes. You may request priority review; however, the Agency will make the final determination of priority review upon evaluation of the proposed application.

5. *Does the Agency agree that it is acceptable to include an OSI (Office of Scientific Investigations) data package from SOLO2 but not Study 19 in the proposed NDA?*

FDA Response:

No. You should provide OSI data packages for each pivotal study included in the proposed NDA.

6. *Does the Agency agree that the proposed risk mitigation strategy adequately addresses potential risks associated with introduction of olaparib tablets to the US market following approval of the proposed NDA?*

FDA Response:

Yes.

7. (b) (4)

FDA Response:

(b) (4)

(b) (4)

8. *AstraZeneca would like to offer an orientation meeting in support of the NDA. Does the Agency wish to have such a session, and if so, when during the review period would this be appropriate?*

FDA Response:

Yes. Within 45 days after arrival of the application, the review team will request an orientation meeting for the purposes of orienting the review team to the content and format of the application.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 10, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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 2 (EOP2) meeting. In the absence of an EOP2 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.

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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 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

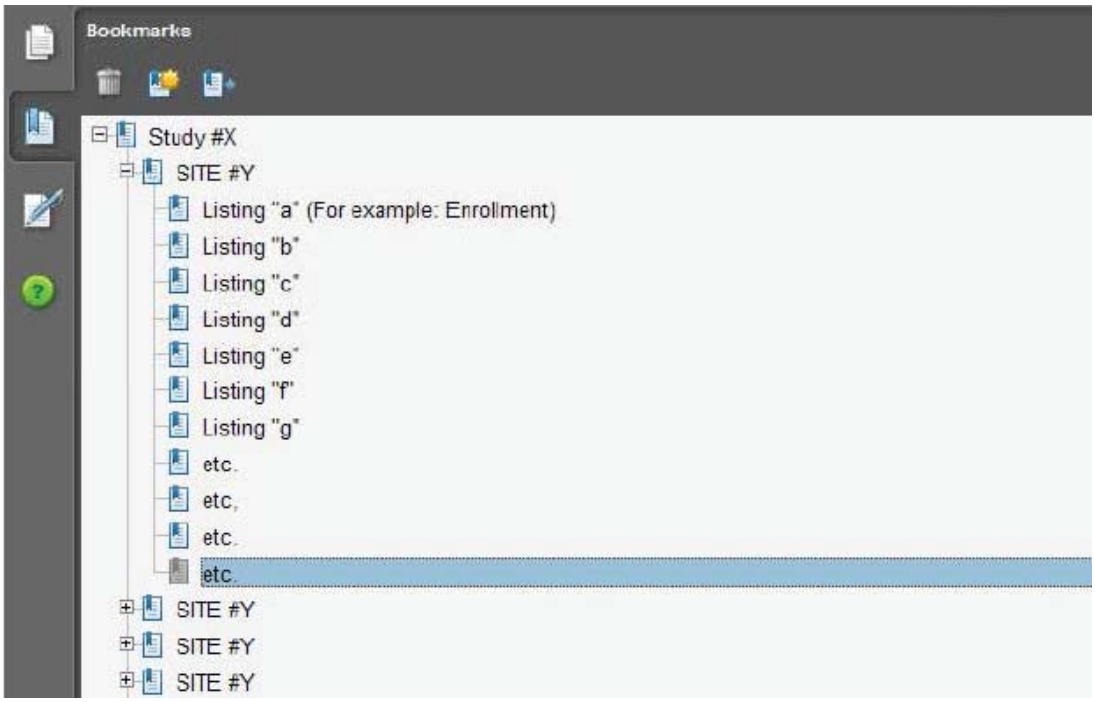
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

   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.

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 Item[1]	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

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

/s/

RAJESH VENUGOPAL
01/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075918

DENY -
BREAKTHROUGH THERAPY DESIGNATION

AstraZeneca Pharmaceuticals LP
Attention: Darci L. Bertelsen
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bertelsen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Olaparib (AZD2281, KU-0059436).

We also refer to your March 19, 2013, request for Breakthrough Therapy designation for (b) (4) ovarian cancer patients.

(b) (4)

Therefore, designation as a Breakthrough Therapy cannot be granted at this time.

(b) (4)

(b) (4)

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA). A guidance document is currently under development.

For further information regarding Fast Track, refer to the guidance for industry Fast Track Drug Development Programs – Designation, Development, and Application Review.

If you have any questions, contact Rajesh Venugopal, Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, MD, MS
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/

AMNA IBRAHIM
05/15/2013
For Dr Robert Justice