CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206162Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206162 SUPPL # HFD # 150

Trade Name Lynparza

Generic Name Olaparib

Applicant Name AstraZeneca

Approval Date, If Known December 19, 2014

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)

c) 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:

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d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

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

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

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

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summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

(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?

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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: Regulatory Health Project Manager

Name of Office/Division Director signing form: Amna Ibrahim, MD
Title: Acting Division Director

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
12/19/2014

AMNA IBRAHIM
12/19/2014

1.3.3 DEBARMENT CERTIFICATION

Re: **NDA 206162**

Olaparib Capsules

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,

Barry Sickels, Vice President
US Regulatory Affairs
AstraZeneca

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206162 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lynparza Established/Proper Name: Olaparib Dosage Form: 50 mg Capsules		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):
RPM: Rajesh Venugopal		Division: DOP1

NDAs and NDA Efficacy Supplements:

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

(For additional information regarding 505(b)(2)s, please refer to http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (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. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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 • User Fee Goal Date is October 3, 2014 (3 Month Extension to January 3, 2015)	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (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., nrew listed drug, patent certification revised).

❖ 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 _____	☒ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME Type 1

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ 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
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other BURST

[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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

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(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
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(s) and date(s) Accelerated Approval 12.19.14
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.	12.10.14
• Original applicant-proposed labeling	2.3.14
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

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❖ 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.	12.10.14
• Original applicant-proposed labeling	2.3.14
• Example of class labeling, if applicable	N/A
❖ 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	11.3.14
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptability letter dated 7.31.14 Review dated 7.21.14
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 4.4.14 ☒ DMEPA 10.21.14 ☒ DMPP/PLT (DRISK) 10.29.14 ☒ OPDP (DDMAC) 10.30.14 ☐ SEALD ☐ CSS N/A ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	4.8.14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 12.19.14
❖ 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
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7.29.14 If PeRC review not necessary, explain: *Ovarian cancer (non-germ cell) is one of the listed indications in the FDA draft "Guidance for Industry: How to Comply with the Pediatric Research Equity Act", September 2005, for which a disease-specific pediatric waiver is granted without requiring justification.* • Pediatric Page/Record *(approvals only, must be reviewed by PERC before*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

finalized)	
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	12.9.14 (2), 12.8.14, 12.5.14, 11.25.14 (2), 11.24.14 (2), 11.20.14, 11.19.14, 11.18.14 (2), 11.13.14, 11.10.14, 11.4.14, 10.31.14, 10.30.14, 10.28.14, 10.27.14, 10.23.14, 10.15.14, 10.9.14, 9.15.14, 9.12.14, 9.5.14, 8.28.14, 8.11.14, 8.6.14, 7.28.14, 7.25.14, 7.16.14 (2), 7.10.14, 7.7.14, 6.24.14, 6.18.14, 6.16.14, 6.13.14, 6.12.14, 6.11.14, 6.9.14 (2), 6.5.14 (2), 6.4.14 (2), 5.30.14, 5.29.14, 5.22.14, 5.12.14, 5.8.14, 5.6.14, 5.1.14, 4.18.14, 4.16.14, 4.14.14 (2), 4.10.14, 4.3.14, 3.14.14 (2), 3.12.14 (2), 2.28.14, 2.19.14, 2.12.14, 2.10.14,
❖ Internal memoranda, telecons, etc.	9.15.14 (telecon), 7.1.14 (telecon)
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• 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 10.2.2013
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Late Cycle meeting scheduled for 12.2.14 was cancelled per Sponsor's request.
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	6.25.14
• 48-hour alert or minutes, if available *(do not include transcript)*	Quick Minutes 7.2.14
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 12.19.14
Division Director Summary Review *(indicate date for each review)*	☐ None 12.16.14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12.10.14
PMR/PMC Development Templates *(indicate total number)*	☐ None 5 PMRs; 1 PMC

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Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	12.4.14(Concurrence with Primary Review)
• Clinical review(s) *(indicate date for each review)*	12.4.14 (Safety); 12.3.14 (Eff.); 4.3.14 (Filing Review)
• 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)*	12.4.14 (In Clinical review, pg.18)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 12.19.14 (CDRH); QT IRT 11.18.14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ 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 ☒ None 11.19.14
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 9.3.14, 7.28.14
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 11.21.14 (Concurrence with Primary Review)
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 11.21.14 (Concurrence with Primary Review)
Statistical Review(s) *(indicate date for each review)*	☐ None 11.21.14, 3.7.14 (filing Review)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None 11.26.14 (Concurrence with Primary Review)
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 11.25.14 (Concurrence with Primary Review)
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11.25.14; 4.4.14 (Filing Review)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None N/A

[6] Filing reviews should be filed with the discipline reviews.

Reference ID: 3676098

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 12.2.14
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12.1.14, 11.21.14 (Concurrence with Primary Review)
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11.21.14, 3.6.14 (Filing Review)
❖ 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)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 12.12.14
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 12/8/14 (Drug Substance (Concurrence with Primary Review)); 12/9/14 (Drug Product (Concurrence with Primary Review))
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 11/25/15 (BioPharm)12/8/14 (Drug Substance; 12/9/14 (Drug Product), 2.24.14 (Filing Review)
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 2.12.14 N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None BioPharm 11-25-14
❖ 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)*	12/9/14 (Drug Product Review, pg. 47)
☐ Review & FONSI *(indicate date of review)*	N/A
☒ Review & Environmental Impact Statement *(indicate date of each review)*	12/9/14 (Drug Product Review, pg. 47)

Reference ID: 3676098

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 11.21.14 3.14.14(Filing Review) ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed 8.2014 ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3676098

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/s/

RAJESH VENUGOPAL
12/19/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 CMC Information Request
Date: Tuesday, December 09, 2014 9:43:50 AM
Attachments: LOA_156_70_49_164_Exchange_05-13-2014_14-20-07.pdf

---

Hi Darci,

Our CMC team reminds you that if you have not done so already, please submit to your NDA the attached LOA for DMF (b) (4). You provided this by email back in June but we don't think it was submitted officially to the NDA.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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

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/s/

RAJESH VENUGOPAL
12/09/2014

From:	Venugopal, Rajesh
To:	darci.bertelsen@astrazeneca.com
Subject:	NDA 206162 (Olaparib) - Request for Minor PI changes
Date:	Tuesday, December 09, 2014 3:03:07 PM

HI Darci,

As we are finalizing the NDA, we found the following on the PI:

Throughout labeling, the cross-references should be BEFORE the period, all in italics (including the parentheses), with lower case “see”. Please make these changes throughout the labeling and submit as soon as possible.

Once fixed, unfortunately it will need to be submitted again through the gateway. Sorry about that. Please let me know when you submitted this through the gateway.

Thank you,
rajesh

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
12/09/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) CMC Information Request
Date: Monday, December 08, 2014 2:07:00 PM

HI Darci,

Upon review our CMC team is asking that you please update the P 5.4 Drug Product Batch Analysis Table 1 titled "Summary of batches of Olaparib capsules 50 mg manufactured at Patheon Pharmaceuticals Inc" with the LMG lots, as submitted in response to our Information Request.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
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/s/

RAJESH VENUGOPAL
12/08/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Cc: Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Subject: FW: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package
Date: Friday, December 05, 2014 2:53:37 PM
Attachments: Marketing, US, P5-01 Specification(s) for Drug Product, olaparib, capsule, 50 mg, bottle1.pdf

Hi Darci,

Can you confirm with me if you have submitted the attached new version of the drug product specs officially through the gateway? If not, can you tell me when you plan to submit the new version to the NDA. We will need that in place to finalize the CMC review of the NDA.

Thank you,
rajesh
.

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, November 24, 2014 12:45 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Rajesh,

AstraZeneca agree to comply with the FDA conditions outlined in the 3 outstanding substantive CMC review issues listed in the Late Cycle Meeting Background Package, namely;

- Acceptance criteria for degradant (b) (4)
- (b) (4) testing
- Stability study as post-marketing commitment

Additional detail around the AstraZeneca position and proposals are presented below;

1. The proposed NMT (b) (4) % acceptance criteria for the content of the degradant, (b) (4), in olaparib capsules at end of expiry is not qualified. FDA advises that the acceptance criteria should be (b) (4) %.
Please note that the acceptance criteria has been set at (b) (4) % in line with the ICH Q3B qualification threshold for degradants in drug product. A revised specification Module 3.2.P.5.1. Specifications is attached.

2. The proposed exclusion of (b) (4) testing for (b) (4) at release of olaparib capsules is not acceptable. FDA advises that insufficient data have been provided to support the exclusion of (b) (4) testing and that all lots should be tested at release.
A revised specification Module 3.2.P.5.1. Specifications is attached reflecting that (b) (4) testing will be routinely performed at release.

3. As a post-marketing commitment, conduct a stability study with the process validation batches (3) with ICH primary stability testing to the submitted specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to (b) (4) months.

This commitment, included in the initial NDA, was the subject of a recent interaction (sequence 0056) where AstraZeneca re-confirmed its approach to conduct a repeat ICH stability study on the process validation batches and agreed mutually acceptable delivery dates for interim and final study reports. Please note the study will be performed up until (b) (4) months which is the agreed drug product shelf-life.

Regarding review issue 1, the Agency has stated that its position on this limit is driven by a lack of qualification of the degradant by toxicological studies or clinical experience. AstraZeneca is (b) (4) For this, and in accordance with ICH guidance (ICH Q3B (R2) Impurities in New Drug Products, 2006), AstraZeneca would (b) (4) . AstraZeneca considers that conducting further genotoxicity studies for the degradant to be unnecessary, as in SAR evaluation this degradant was shown to possess no alerts of concern, and olaparib itself has been shown to be genotoxic through its mechanism of action (PARP inhibition).

Whilst AstraZeneca currently proposes to accept a (b) (4) % end of life specification as the Agency requests, AstraZeneca would like to confirm that (b) (4) .

Please could the Agency provide written confirmation that this approach is an acceptable (b) (4) degradant specification?

If written confirmation is received in advance of the December 2, 2014 Late Cycle Review Meeting, then AstraZeneca will decline the meeting.

If the Division is unable to provide written confirmation in advance of the scheduled meeting on December 2, 2014, then AstraZeneca requests that the meeting format be a teleconference. The proposed AstraZeneca participants are:

Hesham Abdullah – Regulatory Vice President, Oncology Therapy Area
Debbie Mackenzie – Global Regulatory Affairs Director
Roy Jamieson – CMC Regulatory Affairs Director
Jim Murray – Pharmaceutical Development, Project Director
Steve Horner – Nonclinical Principal Scientist
Kieran McKillop – Global Supply Chain
Tony Ho – Global Product Vice President
Darci Bertelsen – US Regulatory Affairs Director

Lastly, based upon the proposed AstraZeneca attendees and the limited scope of the meeting, would it be possible to move the teleconference to the morning hours as several of the team members are located in Europe.

Thanks in advance, and as always, please don't hesitate to contact me if you need any additional information.

Darci Bertelsen
Regulatory Affairs Director

AstraZeneca
GRAPSQA | Regulatory Affairs
1800 Concord Pike, Wilmington DE, 19802

T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:59 PM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Dec. 2, 3-4 PM

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Thursday, November 20, 2014 3:43 PM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Can I ask a quick question.

What time during the day is the meeting scheduled for?

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:30 PM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Hi Darci,

Attached please find our briefing package for the Late Cycle meeting scheduled currently for December 2. Once you've had a chance to review the document please let me know if you still require a face to face meeting or if a teleconference would be enough. If you feel you do not

require either one and you are fine with what's stated in the document then please let me know as well. A copy of this document is also being mailed to you.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

P.5 CONTROL OF DRUG PRODUCT

P.5.1 SPECIFICATION(S) FOR DRUG PRODUCT

The specification for olaparib 50 mg capsule is presented.

Test procedure	Acceptance criteria	Method reference
Description	White to off-white size 0 capsules marked with 'OLAPARIB 50 mg' and the AstraZeneca logo printed in black ink	Description by visual inspection
Identification	Consistent with the retention time and UV spectrum of the reference standard	Identification by LC-UV
(b) (4)	NMT (b) (4)% w/w of olaparib	(b) (4)
Assay	(b) (4)% of label claim	Assay by LC
Degradation products		Degradation products by LC
(b) (4)	NMT (b) (4)% w/w	
Largest individual unspecified degradation product	NMT (b) (4)% w/w	
Total degradation products	NMT (b) (4)% w/w	
Dissolution	Shall comply with the requirements of the United States Pharmacopeia: Q= (b) (4)% at 45 minutes and mean NLT (b) (4)% at 30 minutes	Dissolution Apparatus 2, LC/UV measurement
Uniformity of dosage units	Shall comply with the requirements of the United States Pharmacopeia	Content uniformity by LC
(b) (4)		

NMT Not more than.
NLT Not less than.

Reference ID: 3668858

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RAJESH VENUGOPAL
12/05/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Clinical Pharmacology Additional Information for the Label
Date: Tuesday, November 25, 2014 3:10:56 PM

Hi Darci,

Our clinical pharmacology team wanted the following to be brought to your team's attention and would like the below language be added to the label:

We note that you submitted preliminary PK data for Trial D0816C00006 showing a 1.5 fold increase in AUC in patients with mild renal impairment (N=14). As such, an effect in patients with moderate and severe renal impairment cannot be ruled out before the dedicated trial. Therefore, we recommend you update labeling language in Sections 8 and 12.3 accordingly. Please include this in your response to labeling that is due by Wednesday 12 PM, November 26. You can consider using the following language:

Section 8: A 1.5 fold increase in exposure (AUC) was observed in patients with mild renal impairment (CLcr = 50 - 80 mL/min) compared to patients with normal renal function (CLcr > 80 mL/min). No dose adjustment to the starting dose is required in patients with CLcr of 50 to 80 mL/min, but patients should be monitored closely for toxicity. [redacted (b) (4)]. There are no data in patients with moderate or severe renal impairment (CLcr < 50 mL/min) or patients on dialysis.

Section 12.3: [redacted (b) (4)] a dedicated renal impairment trial, the AUC and Cmax of olaparib increased by 1.5- and 1. 2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50 - 80 mL/min; N=14) compared to those with normal renal function (CLcr > 80 mL/min; N=8). [redacted (b) (4)] There are no data in patients with CLcr < 50 mL/min or in patients on dialysis.

Along with the minor edits to the PI sent yesterday please include the changes above and submit the updated label by 12 PM tomorrow, November 26.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA

Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
11/25/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package
Date: Tuesday, November 25, 2014 9:29:40 AM

Hello Darci,

The proposed approach to (b) (4) for the degradant, (b) (4), is appropriate. The acceptability of (b) (4) CMC data to support an increase in the specification above (b) (4)% will be determined following our review of (b) (4).

If your group accepts our response and wish not to have a face to face OR a teleconference Late Cycle Meeting then please decline in writing so that we may have documentation of this for our records for this NDA. Please note that if a teleconference is required we unfortunately cannot move the time to the morning hours on December 2.

Regards,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, November 24, 2014 12:45 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Rajesh,

AstraZeneca agree to comply with the FDA conditions outlined in the 3 outstanding substantive CMC review issues listed in the Late Cycle Meeting Background Package, namely;

- Acceptance criteria for degradant (b) (4)
- (b) (4) testing
- Stability study as post-marketing commitment

Additional detail around the AstraZeneca position and proposals are presented below;

1. The proposed NMT (b) (4)% acceptance criteria for the content of the degradant, (b) (4), in olaparib capsules at end of expiry is not qualified. FDA advises that the acceptance criteria should be (b) (4)%.
Please note that the acceptance criteria has been set at (b) (4)% in line with the ICH Q3B qualification threshold for degradants in drug product. A revised specification Module 3.2.P.5.1. Specifications is attached.

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provided to support the exclusion of (b) (4) testing and that all lots should be tested at release.

A revised specification Module 3.2.P.5.1. Specifications is attached reflecting that (b) (4) testing will be routinely performed at release.

3. As a post-marketing commitment, conduct a stability study with the process validation batches (3) with ICH primary stability testing to the submitted specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to (b) (4) months.

This commitment, included in the initial NDA, was the subject of a recent interaction (sequence 0056) where AstraZeneca re-confirmed its approach to conduct a repeat ICH stability study on the process validation batches and agreed mutually acceptable delivery dates for interim and final study reports. Please note the study will be performed up until (b) (4) months which is the agreed drug product shelf-life.

Regarding review issue 1, the Agency has stated that its position on this limit is driven by a lack of qualification of the degradant by toxicological studies or clinical experience. AstraZeneca is (b) (4) For this, and in accordance with ICH guidance (ICH Q3B (R2) Impurities in New Drug Products, 2006), AstraZeneca would (b) (4) . AstraZeneca considers that conducting further genotoxicity studies for the degradant to be unnecessary, as in SAR evaluation this degradant was shown to possess no alerts of concern, and olaparib itself has been shown to be genotoxic through its mechanism of action (PARP inhibition).

Whilst AstraZeneca currently proposes to accept a (b) (4)% end of life specification as the Agency requests, AstraZeneca would like to confirm that (b) (4) .

Please could the Agency provide written confirmation that this approach is an acceptable (b) (4) degradant specification?

If written confirmation is received in advance of the December 2, 2014 Late Cycle Review Meeting, then AstraZeneca will decline the meeting.

If the Division is unable to provide written confirmation in advance of the scheduled meeting on December 2, 2014, then AstraZeneca requests that the meeting format be a teleconference. The proposed AstraZeneca participants are:

Hesham Abdullah – Regulatory Vice President, Oncology Therapy Area
Debbie Mackenzie – Global Regulatory Affairs Director
Roy Jamieson – CMC Regulatory Affairs Director
Jim Murray – Pharmaceutical Development, Project Director
Steve Horner – Nonclinical Principal Scientist
Kieran McKillop – Global Supply Chain
Tony Ho – Global Product Vice President
Darci Bertelsen – US Regulatory Affairs Director

Lastly, based upon the proposed AstraZeneca attendees and the limited scope of the meeting, would it be possible to move the teleconference to the morning hours as several of the team members are located in Europe.

Thanks in advance, and as always, please don't hesitate to contact me if you need any additional information.

Darci Bertelsen

Regulatory Affairs Director

AstraZeneca
GRAPSQA | Regulatory Affairs
1800 Concord Pike, Wilmington DE, 19802
T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:59 PM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Dec. 2, 3-4 PM

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Thursday, November 20, 2014 3:43 PM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Can I ask a quick question.

What time during the day is the meeting scheduled for?

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:30 PM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Hi Darci,

Attached please find our briefing package for the Late Cycle meeting scheduled currently for December 2. Once you've had a chance to review the document please let me know if you still require a face to face meeting or if a teleconference would be enough. If you feel you do not require either one and you are fine with what's stated in the document then please let me know as well. A copy of this document is also being mailed to you.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
11/25/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Label
Date: Monday, November 24, 2014 5:05:37 PM
Attachments: annotated-draft-labelNov242014.doc

Hello Darci,

Attached please find our latest edits to the PI. If you are fine with the edits please accept all of the changes and send back to finalize. Please respond by Wednesday 12 PM, November 26, if not sooner.

Thank you,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Wednesday, November 19, 2014 10:18 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Label

Hi Rajesh,

I have attached an annotated and nonannotated label. The team has made two slight modifications to the PI.

- It was noted that there was as discrepancy between Section 2.3 and the Highlights. The wording regarding dose interruptions was modified to reflect how physicians were advised to treat patients in the clinical trials and is now consistent with the statement in the Highlights section.
- The team felt the statement in Section 14 regarding the companion diagnostic needed some additional clarity, so that statement has been modified.

Please let me know if the Division agrees with these changes. If so, then I think we can close this part of the NDA review.

Thanks

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, November 18, 2014 8:53 AM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Label

Hi Darci,

Attached please find our latest round of edits to the PI and Med guide. If you are fine with the edits please accept all of the changes and send back so that we may wrap up this portion of our review of your NDA and hope take an action by Dec. 19. Please respond by 12 PM tomorrow (Nov. 19), if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
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/s/

RAJESH VENUGOPAL
11/24/2014

From: Bertelsen, Darci L
To: Venugopal, Rajesh
Subject: RE: NDA 206162 (Olaparib) Post Marketing Requirements
Date: Monday, November 24, 2014 10:52:04 AM

We will do that.

It will be included in a submission coming to you tomorrow.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, November 24, 2014 9:34 AM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 (Olaparib) Post Marketing Requirements

Received. Thank you Darci. Please submit officially, if you would.
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, November 24, 2014 9:15 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Post Marketing Requirements

Hi Rajesh,

AstraZeneca is in agreement with the proposed timing for this PMC.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, November 21, 2014 1:29 PM
To: Bertelsen, Darci L
Cc: Chlysta, Lori A

Subject: RE: NDA 206162 (Olaparib) Post Marketing Requirements

Hello Darci,

We had a chance to review the PMC timeline internally and we are proposing the following, as we require specific month and year:

PMC Schedule Milestones:	**First Interim Report (includes 6 months of data):**	**11/15**
	Second Interim Report (includes 12 months of data):	**05/16**
	Study Completion:	**02/17**
	Final Report Submission:	**04/17**

Please let me know if you agree by 12 PM Monday, November 24., if not sooner.

Thank you,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, November 21, 2014 8:44 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Post Marketing Requirements

Hi Rajesh,

Below are the AstraZeneca proposed timings for post marketing commitment 2824-6.

2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) *up to end of expiry.*

AstraZeneca Response:

PMC Schedule Milestones:	**Study Completion:**	**February 2017**
	Final Report Submission:	**April 2017 (revised Module 3.2.P.8 containing up to (b) (4) month data**
	Other: Data Submission:	**1Q 2016 (up to (b) (4) month data) 2015 Annual Report**
		1Q 2017 (up to (b) (4) month data) 2016 Annual Report

As always, don't hesitate to contact me if you need anything else.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Wednesday, November 19, 2014 2:07 PM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Post Marketing Requirements

Hi Darci,

Due to the 3 month extension that was given for this NDA review, our goal was to communicate postmarketing requirements/commitments to you by November 1, 2014.

We've mutually agreed to the 5 PMRs however upon further internal discussions, there is 1 postmarketing commitment that require your agreement:

2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

PMC Schedule Milestones:

Study Completion:	AZ to propose
Final Report Submission:	AZ to propose
Other: Data Submission:	At each timepoint

Please provide month and year for each timepoint data will be submitted. Please respond via email by 10 AM Friday November 21, 2014 (if not sooner), with a proposal of the month and year for each milestone above so that we may discuss internally.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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Office of Hematology and Oncology Products
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/s/

RAJESH VENUGOPAL
11/24/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Post Marketing Requirements
Date: Wednesday, November 19, 2014 2:06:43 PM

Hi Darci,

Due to the 3 month extension that was given for this NDA review, our goal was to communicate postmarketing requirements/commitments to you by November 1, 2014.

We've mutually agreed to the 5 PMRs however upon further internal discussions, there is 1 postmarketing commitment that require your agreement:

2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

PMC Schedule Milestones:

Study Completion:	AZ to propose
Final Report Submission:	AZ to propose
Other: Data Submission:	At each timepoint

Please provide month and year for each timepoint data will be submitted. Please respond via email by 10 AM Friday November 21, 2014 (if not sooner), with a proposal of the month and year for each milestone above so that we may discuss internally.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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RAJESH VENUGOPAL
11/19/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (olaparib) Biopharmaceutics Information Request
Date: Tuesday, November 18, 2014 3:35:09 PM
Attachments: image001.png

Hello Darci,

Please find the following information request from our biopharmaceutics team:

"The batch numbers of Olaparib Capsules used in Study D0810C00042, which is now the definitive clinical study, are in the Table below:

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Olaparib	50 mg ×8 capsules orally twice daily	(b) (4) on behalf of AstraZeneca	F13579	8525.1/1, 8525.2/1, 8525.3/1, 8525.4/1, 8525.5/1, 8525.6/1, 8525.7/1, 8525.8/1, 8525.9/1, 8525.10/1, 8525.11/1, 8525.12/1, 8525.17/1.

Provide the following:

- The individual vessel dissolution profile data
- Composite plots of release dissolution profiles of all batches used in clinical study D0810C00042;
- Compare the mean dissolution profiles of these batches to those used in Study D0810C00019 to demonstrate similarity. Present the data graphically and in tabular format;
- The Scatter plots of individual vessel data at 30 min and 45 min for all batches used in Study D0810C00042

Please provide your response to this Biopharmaceutics information request by 12 PM Friday November 21, 2014."

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
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RAJESH VENUGOPAL
11/18/2014

From:	Venugopal, Rajesh
To:	darci.bertelsen@astrazeneca.com
Subject:	NDA 206162 (Olaparib) Label
Date:	Tuesday, November 18, 2014 8:53:21 AM
Attachments:	annotated-draft-labelNov2014.doc

Hi Darci,

Attached please find our latest round of edits to the PI and Med guide. If you are fine with the edits please accept all of the changes and send back so that we may wrap up this portion of our review of your NDA and hope take an action by Dec. 19. Please respond by 12 PM tomorrow (Nov. 19), if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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RAJESH VENUGOPAL
11/18/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Medication Guide
Date: Thursday, November 13, 2014 12:22:34 PM
Attachments: LYNPARZA updated MG.doc

Hi Darci,

As promised attached please find the medication guide for your review and comments, if any. Please return the med guide by Monday 12 PM, November 17, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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OND/CDER/FDA
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RAJESH VENUGOPAL
11/13/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Updated Package Insert
Date: Monday, November 10, 2014 4:37:01 PM
Attachments: annotated-draft-PI Sent Back to AZ_11.10.14.doc

Hi Darci,

Attached please find our edits and comments made to the PI that you submitted on 10/31. I am only providing the PI as our Patient labeling folks are reviewing the medication guide separately. I should have the med guide to you by Thursday at the latest. Please respond to the PI edits and comments by no later than 1 PM Thursday, November 13.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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RAJESH VENUGOPAL
11/10/2014

From:	Venugopal, Rajesh
To:	darci.bertelsen@astrazeneca.com
Subject:	NDA 206162 (Olaparib) - CLinical, CLinPharm, Nonclinical Information Requests
Date:	Tuesday, November 04, 2014 10:23:33 AM

Hello Darci,

Our review team has the following information requests that require your response:

Nonclinical

Please provide data to support changes in section 12.1 of the Prescribing Information indicating that olaparib is an inhibitor of PARP3. Data shown in Table 1, on page 8 of Module 2.6.2 "Nonclinical Written Summary – Pharmacology" in the NDA submission appear inconsistent with data in the referenced journal article [Menear et al (2008) J Med Chem, 51: 6581-6591] which does not show inhibition of PARP3 by olaparib.

Clinical

We are unable to reproduce the lower bound of the 95% CI of the duration of response using SAS9.3. Using K-M estimates and using the variables DUR_RESP for the days of response and CNSR variable for censoring from the Pooled resp analysis dataset, we obtain 166 days (5.5 months) as the lower bound. This number is also obtained when using the data from the adbresp dataset from study 42. We note that you obtain 171 days (5.6 months) as the lower bound. Please provide for how you were able to obtain 171 days.

Clinical Pharmacology

Please submit the study reports which were not submitted with the original NDA for the additional transporters evaluated such as OCT2 and MATE.

Please provide the study reports and responses to the above nonclinical and clinical information requests by 4 PM Friday 11/07/14, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
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RAJESH VENUGOPAL
11/04/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 Olaparib - CMC Information Request
Date: Friday, October 31, 2014 1:38:08 PM

Hello Darci,

In response to the CMC responses you provided yesterday, our CMC team has the following comments for questions 3 and 4 that requires a response by the your team:

> 3. Your response has been reviewed and your proposal to maintain the acceptance criteria for the drug product degradant (b) (4) at (b) (4)% is not acceptable. As previously advised, reduce the acceptance criteria to NMT (b) (4)% at release and on stability.
>
> 4. Your response has been reviewed and your proposal to omit % (b) (4) from drug product testing at release is not acceptable. As previously advised, add characterization of the (b) (4) at release to the drug product specifications.

Please respond by 4 PM Wednesday, November 5.

Thank you,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Thursday, October 30, 2014 2:12 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 Olaparib - CMC Information Request

Hi Rajesh,

I have been informed that the publishing group is experiencing technical difficulties and will not be able to submit the response to this request today. I have attached the response for all the questions except 1b which will be submitted on November 10th as previously agreed.

We will submit this response officially via the gateway as quickly as possible, but I did want to make sure you had the information as requested.

Please let me know if you have any questions.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, October 23, 2014 8:58 AM
To: Bertelsen, Darci L
Subject: NDA 206162 Olaparib - CMC Information Request

Hello Darci,

As mentioned, our CMC team has the following information request that require your response:

1. Drug product expiry:

   a) If available, provide updated stability data for the attribute of (b) (4) in the commercial product lots on stability. The most recent timepoint submitted was 3 months.

   b) For the clinical product (50 mg olaparib capsule), provide the age (months) at the time of administration to the 137 patients with gBRCAm associated ovarian cancer treated with 3 or more lines of chemotherapy in Study 42 between the dates of February 21, 2010 to July 31, 2012.
      i. These data may be provided in excel files with tables listing the lot number, manufacture date, patient, date of administration, age of capsule, number of capsules.
      ii. The response provided for Study 19 in May 2014 would be an acceptable approach for this information request.
      iii. Do not include product dispensed after July 31, 2012
      iv. Include a histogram of the number of capsules versus age of capsule at time of administration (bin size 1 month, mean, median, standard deviation, etc.) for each lot.
      v. Provide a list of the clinical lots administered during this time period.

2. Revise section P.4 Control of Excipients of the NDA to include the specifications for Lauroyl polyoxyl-32 glycerides (LMG) as provided in your response to Q#1 Information Request submitted 25-April-2014 (i.e. Table 1).

3. Reduce the acceptance criteria for the drug product degradant (b) (4). The proposed acceptance criteria of (b) (4)% exceeds the ICH qualification threshold of (b) (4)%, and the degradant is not qualified at this level by toxicological studies or clinical experience. Manufacturing history submitted for 30 clinical lots of olaparib capsules indicate that release and stability levels of this degradant are much lower than the proposed acceptance criteria.

4. Add characterization of the (b) (4) at release to the drug product specifications. It is currently only tested on stability. To date, no data from controlled studies have been provided for % (b) (4) at release or on stability in the clinical or commercial batches. Additional data are needed to support the exclusion of (b) (4) from quality characterization of drug product at release.

Please respond **by 4 PM Thursday, October 30**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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Office of Hematology and Oncology Products
OND/CDER/FDA
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RAJESH VENUGOPAL
10/31/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib Medication Guide
Date: Thursday, October 30, 2014 2:52:53 PM
Attachments: olaparib (LYNPARZA) MG DMPP OPDP Oct 2014 marked copy Submitted to AZ 10.30.14.doc

Hi Darci,

As mentioned yesterday our patient labeling and prescription drug promotion teams does a thorough review of patient package inserts and medication guides that are included with the drug package inserts. I have attached their review of the guide. If you could respond by tomorrow or 12 PM Monday at the latest, we would appreciate it.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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RAJESH VENUGOPAL
10/30/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Post Marketing Requirements
Date: Wednesday, October 29, 2014 1:23:57 PM

Hello Darci,

We refer you to our April 3, 2014, filing communication letter in which we notified you of our target date of August 1, 2014 for communicating postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

Due to the 3 month extension that was given for this NDA review, our goal was to communicate postmarketing requirements/commitments to you by November 1, 2014.

We have the following proposed Postmarketing Requirements for NDA 206162 (Olaparib):

2824-1 Submit the results of 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 (Study D0818C00002, SOLO-2).

PMR Schedule Milestones: Trial Completion: 01/2019

Final Report Submission: 07/2019

2824-2 Conduct and submit the results of 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 (Study D0816C00010).

PMR Schedule Milestones: Trial Completion: 01/2020

Final Report Submission: 07/2020

2824-3 Provide annual summaries of all cases of Acute Myelogenous Leukemia / Myelodysplastic Syndrome identified in patients treated with Lynparza (olaparib). These reports should summarize all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports).

PMR Schedule Milestones:	Annual Summary #1	12/2015
	Annual Summary #2	12/2016
	Annual Summary #3	12/2017
	Annual Summary #4	12/2018
	Annual Summary #5	12/2019
	Final Report Submission:	06/2020

2824-4 Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment".

PMR Schedule Milestones:	Final Protocol Submission:	10/2014
	Trial Completion:	12/2015
	Final Report Submission:	07/2015

2824-5 Submit the final report for trial D0816C00005 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment."

PMR Schedule Milestones:	Final Protocol Submission:	10/2014
	Trial Completion:	12/2015
	Final Report Submission:	07/2015

Please respond via email by 4 PM Wednesday November 5, 2014, if you accept the PMRs with the time table given, as well as provide a formal submission indicating your acceptance. Otherwise, please provide me with a counter-proposal so that we may discuss internally by November 5.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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/s/

RAJESH VENUGOPAL
10/29/2014

From:	Venugopal, Rajesh
To:	"Bertelsen, Darci L"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 2016162 (Olaparib) Edits to the PI, Med Guide, Carton and Container
Date:	Tuesday, October 28, 2014 3:58:37 PM
Attachments:	FDA Response to olaparib label query on safety tables_10.28.14.pdf

Hi Darci,

Please see attached document, which outlines how the clinical team derived Tables 1-4 in the label.
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Tuesday, October 28, 2014 11:06 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 2016162 (Olaparib) Edits to the PI, Med Guide, Carton and Container

Hi Rajesh,

The olaparib team is working on the label with the goal of having it back to you on Friday.

It would be very helpful to us if you could explain to us how you derived the data for Tables 1, 2, 3 and 4; and what criteria was used for combining terms.

This information will help us understand the data being presented and where the numbers are coming from.

If we could have this information by 9 am tomorrow (October 29, 2014), that would be wonderful.

Thanks

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, October 27, 2014 10:52 AM
To: Bertelsen, Darci L
Subject: NDA 2016162 (Olaparib) Edits to the PI, Med Guide, Carton and Container

Hi Darci,

Attached please find our edits to the PI and medication guide. In addition, we also have comments listed below for the carton and container labels.

Carton and Container labeling Comments

1. The established name for drug products should include the finished dosage form.[1] Relocate the dosage form statement so that it immediately follows the established name on the principal display panel (PDP) as such:

Lynparza
(Olaparib) Capsules

2. Increase the prominence of the strength statement on the principal display panel by removing the (b) (4) background highlighting the net quantity statement. As currently presented, the prominence of the net quantity
statement outweighs the prominence of the strength statement on the PDP. Please note by removing the (b) (4) background highlighting the net quantity statement, the (b) (4) font color on the proposed (b) (4) background may not provide adequate contrast for legibility. Consider revising the font color of the net quantity statement.

3. Due to the large quantity of capsules a patient must take for the recommended dose (eight capsules), there is the potential for a patient or caregiver to manipulate the capsules (e.g. open or break the capsules) if the patient
has difficulty swallowing. We recommend, if space allows, adding the statement "Swallow capsule whole. Do not chew, dissolve or open capsule" on the side panel of the container labels, and on the
PDP of the carton labeling.

4. Add the following statement to the carton and container: "Do not expose to temperatures greater than 40°C or 104°F."

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft). April 2013. Accessed October 20, 2014 online at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Please respond and return the label (including carton and container) by 12 PM EST Monday, November 3, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

10/28/14

FDA Response to AZ IR regarding derivation of Tables 1-4 in olaparib label:

In general, the primary clinical reviewer makes a clinical judgment as to when to combine preferred terms for specific adverse events into one line within a table. For example, if abdominal pain is an adverse event thought to be associated with a particular drug, we often combine abdominal pain, abdominal discomfort, lower abdominal pain, upper abdominal pain, etc. to give a more complete picture, especially if the pain does not appear to be more localized to a single area of the GI tract. Similarly, if there are multiple different respiratory tract infections captured with different preferred terms (viral URI, URI, LRI, pneumonia, bronchitis), we often combine these to show that respiratory tract infections may be increased with a particular agent, a finding that may not be recognized if the preferred, and related, terms are not combined.

Each of the tables in the label was derived using the AE or lab dataset indicated, with the preferred terms indicated:

Table 1-

Used AE dataset submitted 7/24/14 (submission 0035). Selected patients who received 3 or more lines, got n=220 in the dataset.

Preferred terms for each AE included:

Anemia- also included hemoglobin decreased, anemia macrocytic

Abdominal pain/discomfort- also included abdominal distention, abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, gastrointestinal pain

Decreased appetite

Nausea

Vomiting

Diarrhea

Dyspepsia- also includes gastritis and gastroesophageal reflux

Fatigue/asthenia- also includes malaise

Nasopharyngitis/URI- also includes- pharyngitis, viral URI, respiratory tract infection, rhinitis, allergic rhinitis, rhinorrhea, sinus congestion, respiratory disorder, pulmonary congestion, strep pharyngitis, sinusitis, rhinitis seasonal, upper respiratory tract congestion.

Arthralgia/ musculoskeletal pain- also includes pain in extremity, periarthritis, bone pain, musculoskeletal stiffness, musculoskeletal discomfort, joint swelling, arthritis, joint stiffness

Myalgia- also includes musculoskeletal pain, muscle contracture, muscle spasms, musculoskeletal chest pain, musculoskeletal discomfort, myopathy, muscle tightness, muscle strain, myopathy toxic.

Cough- also productive cough and allergic cough

Table 2-

Used Lab dataset from 7/24/14 submission (0035)- isolated patients gBRCA (BRACMFL= yes), isolated more than 3 prior regimens. (studies 2, 9, 12, 20, 24, 42), NON-baseline labs only.

Decrease in hemoglobin (g/dL)- G1 <120-100; G2 <100-80; G3 <80-61; G4 ≤60.

Decrease in abs neutrophil count (x10^9/L)- LLN used was 1.8 x 10^9/L. G1 <1.8-1.5; G2 <1.5-1.0; G3 <1.0-0.5; G4 <0.5.

Decrease in platelets- (x 10^9/L)- LLN 150 x 10^9/L. G1 <150-75; G2 <75-50; G3 <50-25; G4 <25.

Decrease in lymphocytes- (x 10^9/L)- G1 <1000- 800; G2 <800-500; G3 <500-200; G4 <200.

MCV elevation- no CTC grading available. Upper limit of normal was 98 FL, so G1-4 was anything >98 FL.

Increased creatinine- upper limit normal 106 µmol/L or > 1.3 mg/dL. Used anything > than ULN to derive G1-4. For G3-4, used the ATOXGR column and got n=5 patients with G3-4 creatinine elevation, which is 2% of n=223 patients.

Table 3-

Used ADAE analysis dataset from 5/3014- 0026 (29) submission for Study 19 AEs - isolated gBRCA mutated "yes".

Anemia- included hemoglobin decreased, hematocrit decreased, red cell count decreased, reticulocytosis, anemia macrocytic

Abdominal pain/discomfort- also included abdominal distention, abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, gastrointestinal pain

Decreased appetite

Nausea

Vomiting

Diarrhea

Dyspepsia- also includes gastritis and gastroesophageal reflux

Dysgeusia

Fatigue/ asthenia, lethargy- also malaise

Nasopharyngitis/ pharyngitis, **URI**- also viral URI, respiratory tract infection, rhinitis, allergic rhinitis, rhinorrhea, sinus congestion, respiratory disorder, pulmonary congestion, strep pharyngitis, sinusitis, rhinitis seasonal, upper respiratory tract congestion.

Arthralgia/musculoskeletal pain- also includes pain in extremity, periarthritis, bone pain, musculoskeletal stiffness, musculoskeletal discomfort, joint swelling, arthritis, joint stiffness

Myalgia- also musculoskeletal pain, muscle contracture, muscle spasms, musculoskeletal chest pain, musculoskeletal discomfort, myopathy, muscle tightness, muscle strain, myopathy toxic.

Back pain- also chondropathy, intervertebral disc protrusion, neck pain

Dizziness- also vertigo, balance disorders, gait disturbance, vertigo positional

Headache- includes migraine, migraine with aura, sinus headache, tension headache

Cough- includes productive cough

Dermatitis/rash- includes allergic dermatitis, contact dermatitis, pain of skin, erythema, exfoliative rash, generalized erythema, rash, rash erythematous, rash general, rash macular, rash papular, rash maculopapular, rash pruritic, skin discoloration, skin induration, skin lesion

Table 4

Used ADLB dataset, selected for gBRCA mutated, nonbaseline values only.

Decrease in hemoglobin (g/dL)- G1 <120-100; G2 <100-80; G3 <80-61; G4 ≤60.

Decrease in abs neutrophil count (x10^9/L)- LLN used was 1.8 x 10^9/L. G1 <1.8-1.5; G2 <1.5-1.0; G3 <1.0-0.5; G4 <0.5.

Decrease in platelets- (x 10^9/L)- LLN 150 x 10^9/L. G1 <150-75; G2 <75-50; G3 <50-25; G4 <25.

MCV elevation- no CTC grading available. Upper limit of normal was 98 FL, so G1-4 was anything >98 FL.

Increased creatinine- upper limit normal 106 µmol/L or > 1.3 mg/dL. Used anything > than ULN to derive G1-4. No G3-4s.

Glucose elevated- Reference range for normal was highly variable, so used ATOXGR column, and derived G1-4 and G 3-4 glucose elevation.

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/s/

RAJESH VENUGOPAL
10/28/2014

From:	Venugopal, Rajesh
To:	darci.bertelsen@astrazeneca.com
Subject:	NDA 2016162 (Olaparib) Edits to the PI, Med Guide, Carton and Container
Date:	Monday, October 27, 2014 10:51:50 AM
Attachments:	10.27.14_nonannotated-draft-label-Lynparza for 4th line OC treatment_Submitted to AZ 10.27.14.doc

Hi Darci,

Attached please find our edits to the PI and medication guide. In addition, we also have comments listed below for the carton and container labels.

Carton and Container labeling Comments

1. The established name for drug products should include the finished dosage form.[1] Relocate the dosage form statement so that it immediately follows the established name on the principal display panel (PDP) as such:

Lynparza
(Olaparib) Capsules

2. Increase the prominence of the strength statement on the principal display panel by removing the (b) (4) background highlighting the net quantity statement. As currently presented, the prominence of the net quantity
statement outweighs the prominence of the strength statement on the PDP. Please note by removing the (b) (4) background highlighting the net quantity statement, the (b) (4) font color on the proposed (b) (4) background may not provide adequate contrast for legibility. Consider revising the font color of the net quantity statement.

3. Due to the large quantity of capsules a patient must take for the recommended dose (eight capsules), there is the potential for a patient or caregiver to manipulate the capsules (e.g. open or break the capsules) if the patient
has difficulty swallowing. We recommend, if space allows, adding the statement "Swallow capsule whole. Do not chew, dissolve or open capsule" on the side panel of the container labels, and on the
PDP of the carton labeling.

4. Add the following statement to the carton and container: "Do not expose to temperatures greater than 40°C or 104°F."

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft). April 2013. Accessed October 20, 2014 online at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Please respond and return the label (including carton and container) by 12 PM EST Monday, November 3, if not sooner.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RAJESH VENUGOPAL
10/27/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib - CMC Information Request
Date: Thursday, October 23, 2014 8:57:35 AM

Hello Darci,

As mentioned, our CMC team has the following information request that require your response:

1. Drug product expiry:

   a) If available, provide updated stability data for the attribute of (b) (4) in the commercial product lots on stability. The most recent timepoint submitted was 3 months.

   b) For the clinical product (50 mg olaparib capsule), provide the age (months) at the time of administration to the 137 patients with gBRCAm associated ovarian cancer treated with 3 or more lines of chemotherapy in Study 42 between the dates of February 21, 2010 to July 31, 2012.
      i. These data may be provided in excel files with tables listing the lot number, manufacture date, patient, date of administration, age of capsule, number of capsules.
      ii. The response provided for Study 19 in May 2014 would be an acceptable approach for this information request.
      iii. Do not include product dispensed after July 31, 2012
      iv. Include a histogram of the number of capsules versus age of capsule at time of administration (bin size 1 month, mean, median, standard deviation, etc.) for each lot.
      v. Provide a list of the clinical lots administered during this time period.

2. Revise section P.4 Control of Excipients of the NDA to include the specifications for Lauroyl polyoxyl-32 glycerides (LMG) as provided in your response to Q#1 Information Request submitted 25-April-2014 (i.e. Table 1).

3. Reduce the acceptance criteria for the drug product degradant (b) (4). The proposed acceptance criteria of (b) (4)% exceeds the ICH qualification threshold of (b) (4)%, and the degradant is not qualified at this level by toxicological studies or clinical experience. Manufacturing history submitted for 30 clinical lots of olaparib capsules indicate that release and stability levels of this degradant are much lower than the proposed acceptance criteria.

4. Add characterization of the (b) (4) at release to the drug product specifications. It is currently only tested on stability. To date, no data from controlled studies have been provided for % (b) (4) at release or on stability in the clinical or commercial batches. Additional data are needed to support the exclusion of (b) (4) from quality characterization of drug product at release.

Please respond **by 4 PM Thursday, October 30**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
10/23/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Cc: Wheeler, Charlene
Subject: NDA 206162 Olaparib - CLinical Information request
Date: Wednesday, October 15, 2014 11:57:22 AM

Hi Darci,

Our clinical team asks the following:

Please provide your estimated study completion date and date of the submission of the study reports for SOLO-2 and for Study D0816C00010. We request a response by the morning of 10/17. Please note that I will be out of the Office until Wednesday Oct. 22 but I have copied Charlene Wheeler who will be covering for me on Friday.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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/s/

RAJESH VENUGOPAL
10/15/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib - CMC Information Request
Date: Thursday, October 09, 2014 3:50:49 PM

Hello Darci,

Our CMC team has the following information request that requires you response:

1. Storage conditions to address the risk of capsule thermal failure:
   Per stability data provided for 50 mg olaparib capsules in P.8.3 Stability Data for the Drug Product Tables 17, 20 and 23, appearance testing reports thermal failure [redacted] (b) (4) for batches 3063386R, 3114165R and 3115337R. The appearance test results report "capsules showed evidence of leakage", "capsule shell has deformed" and "capsule shell has deformed and printing ink smudged suggesting leakage of capsule content" respectively. [redacted] (b) (4) .

   The proposed storage conditions provided in the Package Insert (PI), carton and container labels are not acceptable – the Package Insert (PI) does not include a storage statement in Section 16 and the statement [redacted] (b) (4) on the carton and container labels is incomplete.

   Given the failure of capsules on storage at [redacted] (b) (4) and the [redacted] (b) (4) , there is a significant risk of capsule failure on exposure to uncontrolled high temperatures – for example during shipment to the patient (e.g. via mail order) and during storage by the patient (e.g. in a vehicle at summer temperatures).
   a. Provide an assessment of the risk of thermal failure from product release until the patient takes the capsule. Include an assessment of the risk to patient and others from failed capsules (e.g. sub-potent dosing, unintended transfer of chemotherapeutic agent from leaking capsules).
   b. Propose controls and discuss the effectiveness of the proposed controls.
   c. Include a storage statement, with a minimum, maximum and excursion temperature range, supported by stability data on the

capsules.

d. Revise storage statement(s) in the PI, carton and container labels.

Please respond by **4 PM Thursday, October 16**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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/s/

RAJESH VENUGOPAL
10/09/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 15, 2014

Application Number: NDA 206162
Product Name: Olaparib
Sponsor/Applicant Name: AstraZeneca

Subject: Test for elemental impurities in the specification of Olaparib

FDA Participants
Ali Al Hakim, PhD, ONDQA Branch Chief
Gaetan Ladouceur, PhD, ONDQA CMC Reviewer
Rajesh Venugopal, RPM, DOP1

Sponsor/Applicant Participants
Roy Jamieson, PhD, Global CMC Regulatory Affairs
Jim Murray, PhD, Pharmaceutical Development
Mark Drew, PhD, Pharmaceutical Development
Tony Ho, MD, Global Product Vice President
Debbie Mackenzie, Global Regulatory Affairs
Darci Bertelsen, US Regulatory Affairs

BACKGROUND:

The teleconference conducted is in reference to an information request submitted to the Sponsor on August 11, 2014 and the response provided on August 22, 2014. The Agency requested the following information:

1. In section S.4.5, your justification to exclude a test for elemental impurities in the specification of the drug substance is not acceptable. Include a test and an acceptance criterion for Heavy Metals in the specification of Olaparib drug substance and provide a revised table in section S.4.1.

2. Revise the batch analyses in section S.4.4 for the 6 commercial batches (Tables 10 and 11, batches 11 to 16) to include test results for Heavy Metals.

The response from the Sponsor was not acceptable by the Agency so a teleconference was conducted to clear up and ascertain information.

DISCUSSION:

The agency requested a test and an acceptance criterion for Heavy Metals in the specification of Olaparib drug substance. The agency and the sponsor agreed that a test for class 1 elemental

Reference ID: 3628300

impurities according to the draft ICH Q3D guideline would be acceptable and should be included in the drug substance specification. The Agency asked the sponsor to revise the batch analyses of the 6 commercial batches found in section S.4.4 of the NDA submission to include test results for class 1 elemental impurities.

The agency suggested that during the post-marketing phase and after the Applicant has gained more experience with several commercial batches, a supplement describing a detailed risk assessment of potential elemental impurities in the drug substance with supporting data may be submitted for evaluation.

ACTION ITEMS:

The Sponsor was requested to submit by September 30, 2014 a revised drug substance specification and batch analyses. The Sponsor has committed to do so.

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RAJESH VENUGOPAL
09/16/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Clinical Pharmacology Information Request
Date: Monday, September 15, 2014 11:27:56 AM

Darci,

Our ClinPharm team asks the following:

- Please submit the protocols for Trial D0816C00005 and for other ongoing trials (that have not been submitted) that are planned to be submitted for the clinical pharmacology program for this NDA. Submit these protocols by Friday Sept 19th.

rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Sunday, September 14, 2014 2:15 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Clinical Pharmacology Information Request

Hi Rajesh,

The protocol for trial D0816C00005 was not submitted to any of the olaparib IND's as it is being conducted at 5 sites in Western Europe. If you would like us to submit the protocol to the NDA for informational purposes, we can include it in the submission scheduled for September 18, 2014.

In addition, I was wondering if you had scheduled a late cycle review meeting yet.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, September 12, 2014 1:33 PM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Clinical Pharmacology Information Request

Hi Darci,

Our clin pharm team has the following information requesting requiring a response:

Please specify the IND#, Serial# and date that the protocol for Trial D0816C00005 (Hepatic Impairment Trial) was submitted to through our gateway.

Please respond by 4 PM Monday, Sept. 15.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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RAJESH VENUGOPAL
09/15/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Clinical Pharmacology Information Request
Date: Friday, September 12, 2014 1:33:20 PM

Hi Darci,

Our clin pharm team has the following information requesting requiring a response:

Please specify the IND#, Serial# and date that the protocol for Trial D0816C00005 (Hepatic Impairment Trial) was submitted to through our gateway.

Please respond by 4 PM Monday, Sept. 15.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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RAJESH VENUGOPAL
09/12/2014

From:	Venugopal, Rajesh
To:	"Bertelsen, Darci L"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 206162 (Olaparib) - CMC information request
Date:	Friday, September 05, 2014 4:10:26 PM

Hello Darci,

Below please find team's review of the draft protocol:

This study is unlikely to provide sufficient evidence to support the conversion from accelerated to full approval due to problems in the study design regarding the proposed patient population and control arm, namely:

1. **Patients who "are not indicated to receive further platinum based chemotherapy due to toxicity or require platinum treatment break according to the investigator" is a poorly defined population, and the definition may vary broadly across the 100 different centers in 15 different countries in which this study is planned to be initiated.**
2. **There is a survival advantage associated with the use of a platinum doublet for patients with platinum sensitive disease, so for those patients who have not received 2 lines of platinum-based therapy, the use of non-platinum therapy would be a deviation from the standard of care. It is unclear whether the use of multiple lines of non-platinum containing treatment regimens would attenuate the survival advantage of platinum-based therapy.**
3. **There is potential for bias to be introduced as those patients who have platinum-intermediate (aka partially platinum sensitive) disease would be expected to have a smaller PFS interval as compared to those patients who have platinum sensitive disease that requires a "treatment break".**

To overcome the aforementioned limitations to this study, we advise you conduct this trial in patients who have received more than 2 lines of platinum-based chemotherapy for germline, deleterious BRCA mutation associated ovarian cancer. The primary endpoint of PFS is acceptable in this disease setting providing that the magnitude of effect is clinically relevant and that there is a positive risk-benefit profile of olaparib therapy in this patient population.

Regarding the secondary objective of HRQoL in this open-label study, a double-blind trial design is recommended to reduce bias when key study outcomes are evaluated using clinical outcome assessments (COAs), including patient reported outcomes (PROs). In settings where blinding is not feasible, PRO results will need to provide convincing evidence of treatment effect to overcome the potential influence of bias. In either case, PRO results can be further supported by findings based on other endpoints and by sensitivity or subgroup analyses comparing the findings relative to other data collected in the trial (concomitant medications, adverse event reporting, tumor response, etc.). For instance, reduction in pain intensity measured by a PRO assessment could be further supported by reduced opiate use or could be associated more commonly with patients who had significant tumor responses.

Please note that we may have more comments in the near future.

Regards,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, September 05, 2014 12:38 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) - CMC information request

Thanks Rajesh

Should we still anticipate getting comments on the draft protocol submitted on August 15th?

Darci

Sent via the Samsung Galaxy S™ III, an AT&T 4G LTE smartphone

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-------- Original message --------
From: "Venugopal, Rajesh"
Date:09/05/2014 12:12 PM (GMT-05:00)
To: "Bertelsen, Darci L"
Cc: "Chlysta, Lori A"
Subject: RE: NDA 206162 (Olaparib) - CMC information request

We see it in our database now. Thanks. Will forward it to the CMC team. Have a nice weekend.
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, September 05, 2014 11:42 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) - CMC information request

Hi Rajesh,

This email is just to inform you that the AstraZeneca response to the information request below has been submitted and we have received confirmation that it has gone through the gateway.

Darci

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and

may be unlawful.

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, August 28, 2014 11:47 AM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) - CMC information request

Hi Darci,

Our CMC team has the following information request that require your response:

Your response received on August 22, 2014 related to questions 3 and 4 of the IR dated August 11, 2014, is not acceptable. During the post-marketing phase and after you gained more experience with several commercial batches, you may submit in a supplement your detailed risk assessment and supporting data for evaluation. Therefore, we reiterate the following deficiencies:

1. Include a test and an acceptance criterion for Heavy Metals in the specification of Olaparib drug substance and provide a revised table in section S.4.1.

2. Revise the batch analyses in section S.4.4 for the 6 commercial batches (Tables 10 and 11, batches 11 to 16) to include test results for Heavy Metals.

Please respond by 4 PM Friday, Sept. 5.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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RAJESH VENUGOPAL
09/05/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CMC information request
Date: Thursday, August 28, 2014 11:46:36 AM

Hi Darci,

Our CMC team has the following information request that require your response:

Your response received on August 22, 2014 related to questions 3 and 4 of the IR dated August 11, 2014, is not acceptable. During the post-marketing phase and after you gained more experience with several commercial batches, you may submit in a supplement your detailed risk assessment and supporting data for evaluation. Therefore, we reiterate the following deficiencies:

1. Include a test and an acceptance criterion for Heavy Metals in the specification of Olaparib drug substance and provide a revised table in section S.4.1.

2. Revise the batch analyses in section S.4.4 for the 6 commercial batches (Tables 10 and 11, batches 11 to 16) to include test results for Heavy Metals.

Please respond by 4 PM Friday, Sept. 5.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/s/

RAJESH VENUGOPAL
08/28/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (olaparib) CMC Information Request
Date: Monday, August 11, 2014 10:13:29 AM

Hello Darci,

Our CMC review team has the following information request based on their current review of your original NDA submission sent on February 3, 2014:

1. In section S.2.2.2, provide the following information:
   - Include Normal Operating Ranges for the [redacted] (b) (4) of the drug substance manufacturing process.
   - Provide detailed process parameters and ranges for the [redacted] (b) (4) .
2. In Table 7 of section S.2.4.2, the proposed acceptance criterion for [redacted] (b) (4) in the Olaparib [redacted] (b) (4) specification appears too high based on your submitted batch history. Tighten this acceptance criterion to more accurately reflect your drug substance manufacturing capability.
3. In section S.4.5, your justification [redacted] (b) (4) is not acceptable. Include a test and an acceptance criterion for Heavy Metals in the specification of Olaparib drug substance and provide a revised table in section S.4.1.
4. Revise the batch analyses in section S.4.4 for the 6 commercial batches (Tables 10 and 11, batches 11 to 16) to include test results for Heavy Metals.

Please respond by 4 PM Friday, August 22.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
08/11/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Clinical Pharmacology Information Request
Date: Wednesday, August 06, 2014 8:48:15 AM

Hi Darci,

The Clinical pharmaocology team thanks you for your response sent on July 31, 2014. We look forward to reviewing your updated proposed label.

We have the following comments regarding your proposed timeline sent on July 31st 2014:

- For Trial D081AC00001, you have clarified that the study report submitted for the food effect assessment in Part A was a final report and that you will submit the safety data evaluated in Part B on October 8th. Your plan appears acceptable.
- You plan to submit the final study report for Trial D0816C00004 (Food effect tablet + QT) by August 1st and for Trial D0816C00007 (Itraconazole + QT) by September 18th. In addition, you plan to submit the pooled QT report by October 1st. We request you submit the final study report for Trial D0816C00007 by September 1st to aid in our timely review within this review cycle. For the QT report to be submitted on October 1st, please submit all information requested in the format requested by QT/IRT on June 4th 2014.
- You plan to submit the final study report for Trial D0816C00008 (Rifampacin) on October 20th. Based on your timeline submitted with the NDA submission, data for this trial was expected to be available by June 2nd. If possible, we request the final study report be submitted by September 1st.
- You have not mentioned plans to submit any preliminary data from the organ impairment trials D0816C00005 (Hepatic) and D0816C00006 (Renal). Trial D0816C00006 was planned to begin on November 30th, 2013 and Trial D0816C00005 was planned to begin on February 1st 2014. Please clarify which cohorts of patients you can provide us with preliminary data for by September 1st in both trials.

We would appreciate your effort in providing us the study reports and related datasets in a timely manner. Please respond to our comments on your proposed timeline by Monday August 11th.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171

E-mail: Rajesh.Venugopal@fda.hhs.gov
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/s/

RAJESH VENUGOPAL
08/06/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206162

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

AstraZeneca Pharmaceutical LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

ATTENTION: Darci L. Bertelsen
Director, Regulatory Affairs

Dear Ms. Bertelsen:

Please refer to your New Drug Application (NDA) dated February 3, 2014, received February 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olaparib Capsules, 50mg.

We also refer to your May 9, 2014, correspondence, received May 9, 2014, requesting review of your proposed proprietary name, Lynparza.

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

If any of the proposed product characteristics as stated in your May 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
07/31/2014

PeRC PREA Subcommittee Meeting Minutes
July 16, 2014

PeRC Members Attending:
Lynne Yao
George Greeley
Daiva Shetty
Wiley Chambers
Susan McCune
Rachel Witten
Shrikant Pagay
Tom Smith
Karen Davis Bruno
Susan McCune
Rosemary Addy
Dianne Murphy
Lily Mulugeta
Rachel Witten
Michelle Roth Cline
Rosemary Addy

PREA

10:10	BLA	(b) (4)		
10:30	NDA			
10:50	BLA			
11:10	NDAs			
11:30	NDA			
	NDA			
	NDA	*206162*	*Olaparib Full Waiver (Agreed iPSP for this product)*	*Treatment of ovarian cancer*
	NDA	(b) (4)		

(b) (4)

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

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/s/

GEORGE E GREELEY
07/29/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Clinical Pharmacology Information request
Date: Monday, July 28, 2014 10:38:00 AM

Hello Darci,

Below please find the following information request from our clinical pharmacology team:

Astra Zeneca sent the following response on June 24th to the FDA comments sent on June 18th: **AstraZeneca acknowledges the Division's recommendation and will continue to take this advice into consideration. We acknowledge that some of the increased exposure seen in the presence of food could indeed be due to inter-occasion variability but at this time, in view of the lack of tolerability data in the fed state we still believe that** [redacted] (b) (4) **are appropriate. We are willing to continue to discuss this point with the Division as the review progresses.**

FDA Response (07/28/14): We urge you to [redacted] (b) (4) in the dosage and administration section as you have not provided rationale that [redacted] (b) (4). As you have acknowledged，some of the increased exposure seen in the presence of food could indeed be due to inter-occasion variability. In addition, the steady state exposure of olaparib in the ongoing Phase 3 trial （SOLO-2）using the tablet formulation 300 mg BID appears to be 50% higher as compared to those in study 19 and 42 with the 400 mg capsule 400 mg BID. Therefore, we do not think the food effect would be a big concern. In contrast, the GI tolerability issue is a big concern for us, especially taking into the consideration of the ODAC meeting discussion. We think [redacted] (b) (4) has the potential to improve patient convenience and potentially compliance and tolerability. The results of the food effect trial may be included in Section 12.3 of the label. In addition, we recommend that you amend the protocols of your ongoing clinical trials to remove the food restriction. **Please respond by 4 PM Friday, August 1st**.

In addition, include information on the status of the clinical pharmacology studies. Indicate dates when final study reports for the completed trials and preliminary reports that have not been submitted can be submitted during this review cycle. Prompt action may enable a more informative label and reduce

the number of PMRs to be issued.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
07/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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 New Drug Application (NDA) dated February 3, 2014, received February 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for olaparib, 50 mg capsules.

On July 24, 2014, we received your July 24, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 3, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 27, 2014.

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

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
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
07/25/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) CMC Information Request
Date: Wednesday, July 16, 2014 2:15:20 PM

HI Darci,

Our CMC reviewers have the following request requiring your response:

"Provide a description of all differences between the proposed commercial product and the clinical product administered in the studies to be submitted in the major clinical amendment (e.g. studies 2,9,12, 20, 24 and 42). Include manufacturer, site, process, specifications and any other considerations which may impact quality attributes."

Please respond **by 4 PM Friday, July 18**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
07/16/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: Olaparib Submission
Date: Wednesday, July 16, 2014 11:15:41 AM

Hello Darci,

Our division would like to know if we can expect the major amendment in by this Friday, July 18? If not, can you please provide a timeline expeditiously of the various elements that you will be submitting (i.e. labeling, datasets, study reports, etc.)?
Thank you,
rajesh

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/s/

RAJESH VENUGOPAL
07/16/2014

PeRC PREA Subcommittee Meeting Minutes
July 2, 2014

PeRC Members Attending:
Lynne Yao
George Greeley
Daiva Shetty
Wiley Chambers
Susan McCune
Rachel Witten
Shrikant Pagay
Tom Smith
Karen Davis Bruno
Susan McCune
Rosemary Addy
Dianne Murphy
Lily Mulugeta
Rachel Witten
Michelle Roth Cline
Rosemary Addy

PREA

	NDA	*206162*	*Olaparib Full Waiver (Agreed iPSP for this product)*	*Treatment of ovarian cancer*
	NDA	[redacted] (b) (4)		

Olaparib Full Waiver

NDA 206162 seeks review of Olaparib for the treatment of ovarian cancer

- The application has a PDUFA goal date of July 25, 2014.
- The application triggers PREA as a new: active ingredient, dosage form, dosing regimen, route of administration and indication.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a full waiver because the disease/condition does not occur in pediatric patients.

[redacted] (b) (4)

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/s/

GEORGE E GREELEY
07/15/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 1, 2014

Application Number: NDA 206162
Product Name: Olaparib
Sponsor/Applicant Name: AstraZeneca

Subject: Outcome from ODAC Meeting on June 25, 2014

FDA Participants
Richard Pazdur, MD, Director, OHOP
Amna Ibrahim, MD, Acting Director, DOP 1
Geoffrey Kim, MD, Clinical - Efficacy, DOP1
Gwynn Ison, MD, Clinical – Safety, DOP1

Sponsor/Applicant Participants
Hesham Abdullah, MD, MSc, RAC, VP, Global Regulatory Affairs, Oncology
Darci Bertelsen, BA, US Regulatory Affairs Director
Tony Ho, MD, Global Product Vice President, Olaparib
Briggs Morrison, MD, Eecutive Vice President and Chief Medical Officer
Antoine Yver, MD, MSc, VP, Oncology Head, Global Medicines Development

1.0 BACKGROUND:

An Oncology Drug Advisory Committee (ODAC) meeting was held on June 25, 2014 to discuss NDA 206162. Eleven of 13 members of the ODAC voted that consideration of marketing approval should be delayed until the results of SOLO-2 were available. A teleconference was conducted on July 1, 2014 to discuss the outcome of the ODAC meeting and to discuss how the applicant can address the concerns raised by the ODAC during this review cycle.

2.0 DISCUSSION:

The Applicant provided a summary of their perspective on the concerns raised by the committee members. The Agency then gave constructive criticism and feedback on the Applicant's presentations at the ODAC meeting. The Agency then advised the Applicant to analyze their existing data regarding the safety and efficacy of olaparib in the heavily pretreated, gBRCAm associated ovarian cancer setting. This analysis would consist of a pooled analysis of the clinical activity of olaparib monotherapy in patients with heavily pretreated, gBRCAm associated ovarian cancer in terms of response rates in the single arm Study 42 and other single-arm studies.

3.0 ACTION ITEMS:

The Applicant is to review their study 42 and other clinical trial data and submit a major amendment to the NDA which will extend the PDUFA goal date by 3 months.

Reference ID: 3592084

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RAJESH VENUGOPAL
07/14/2014

From:	Venugopal, Rajesh
To:	"Bertelsen, Darci L"
Cc:	Chlysta, Lori A
Subject:	RE: Olaparib NDA 206162 - Clarification Questions Regarding July 7, 2014 IR
Date:	Thursday, July 10, 2014 4:16:47 PM

Darci,

Below is the review team's response in **RED**.

rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Thursday, July 10, 2014 12:17 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: Olaparib NDA 206162 - Clarification Questions Regarding July 7, 2014 IR

Rajesh,

The AstraZeneca team has reviewed the July 7, 2014 information request regarding the reanalysis of study 42 and would like some clarification to help ensure the responses we provide on July 18th meet the Division's needs.

FDA Information Request 1

The Division's request states "Re-analyze study 42 to ascertain the confirmed, overall response rate and duration of response for patients who have received more than 3 previous chemotherapy regimens. Provide the datasets used to conduct this analysis, specifically including how the number of prior chemotherapy regimens for each patient was determined. Include an analysis of platinum sensitive who were not eligible to receive further platinum patients and platinum resistant patients."

We understand this request to focus on the **gBRCA ovarian patients** included in within study 42. In addition, we are defining the analysis of 'platinum sensitive who were not eligible to receive further platinum' as those patients who relapse more than 6 months after completion of last line platinum chemotherapy and 'platinum resistant patients' as those who relapse less than 6 months after completion of last line of platinum chemotherapy. These definitions are consistent with the definitions used in the clinical study report. ***Please confirm that you agree with our definition of these two analysis populations.***

FDA Response:
Yes, we agree.

FDA Information Request 2

The Division's request states "Perform a pooled analysis of all available data regarding the

response rate of olaparib in gBRCAm patients who have received more than 3 prior chemotherapy regimens. Include an analysis of platinum sensitive and platinum resistant patients. Provide data on the overall response rate, duration of response, and a comprehensive safety analysis. Provide any and all available pharmacokinetic data for these patients."

We understand that this request is for a pooled analysis of all available data for Olaparib 400mg capsule monotherapy in **gBRCA ovarian patients**. For all studies, where data is available (this information wasn't routinely collected in all studies), platinum sensitive patients will be defined as those who relapse more than 6 months after completion of last line platinum chemotherapy and platinum resistant patients are those who relapse less than 6 months after completion of last line of platinum chemotherapy. ***Please confirm this is acceptable.***

FDA Response:
Yes, we agree.

The pool analysis will involve gBRCA ovarian data from studies 2,9,12, 20, 24 and 42. Study 19 will not be included. ***Please confirm this is acceptable.***

FDA Response:
Yes, we agree.

The overall response rate and duration of response data used to support this request will be obtained from the non-CDISC, legacy analysis data created and QC'd at the time of the original CSR for all studies other than study 42. Study 42 will reference the ADaM data submitted as part of the original FDA filing (3rd February 2014). The resulting dataset will be a subject level analysis dataset. This will be clearly documented in the define file and reviewers guide. Given that we are using, in part, non-CDISC, legacy data for this request we plan to complete an additional targeted quality review of this data and will inform the division of any findings. ***Does the Division agree this approach?***

FDA Response:
Yes, we agree.

For the requested comprehensive safety analysis, we propose to provide the following: Safety data from the pool described below, split by early (≤3) and late (4+) lines of therapy, the following outputs will be provided: overall AE category table; AEs by system organ class (SOC) and preferred term (PT); AEs grade 3 and higher by SOC/ PT; SAEs by SOC/PT; AEs leading to dose reduction; AEs leading to dose interruption; AEs leading to discontinuation; Deaths; Additional information on adverse drug reactions; Special topics (MDS/AML and new primary cancers); Shift tables of CTC grade change from baseline for Hb, platelets, neutrophils and lymphocytes. ***Please confirm these are the appropriate comprehensive safety analyses.***

FDA Response:
Yes, we agree.

Lastly, AstraZeneca and Myriad will continue to work with CDRH regarding the PMA, once final decisions are made regarding the NDA.

FDA Response:

AstraZeneca and Myriad should continue to work on the PMA and not wait until a final decision is made regarding the NDA. The updated analysis of Study 42 and the pooled analysis of Olaparib 400 mg monotherapy will likely be considered a major amendment and will extend the PDUFA date by 3 months. There is still the expectation for a simultaneous approval of the NDA and PMA if olaparib is approved.

Darci Bertelsen
US Regulatory Affairs Director

AstraZeneca
GRA | US Regulatory Affairs
C2C-717, 1800 Concord Pike, Wilmington DE, 19802
T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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RAJESH VENUGOPAL
07/10/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CLinical Information Request
Date: Monday, July 07, 2014 8:54:22 AM

Hi Darci,

Below please find the following clinical request for information requiring response:

1. Re-analyze study 42 to ascertain the confirmed, overall response rate and duration of response for patients who have received more than 3 previous chemotherapy regimens. Provide the datasets used to conduct this analysis, specifically including how the number of prior chemotherapy regimens for each patient was determined. Include an analysis of platinum sensitive who were not eligible to receive further platinum patients and platinum resistant patients.
2. Perform a pooled analysis of all available data regarding the response rate of olaparib in gBRCAm patients who have received more than 3 prior chemotherapy regimens. Include an analysis of platinum sensitive and platinum resistant patients. Provide data on the overall response rate, duration of response, and a comprehensive safety analysis. Provide any and all available pharmacokinetic data for these patients.
3. Provide an updated USPI reflecting the above analyses. All sections of the label should be changed to reflect the revised indication and population.
4. Perform a comprehensive literature search to determine the reported response rates for approved and non-approved agents in ovarian cancer patients who have received more than 3 lines of chemotherapy.
5. Provide details regarding the gBRCAm status of the patients on study 42 and on the additional patients included in the pooled analysis. Provide how many of these patients underwent testing with the Myriad test and indicate how many samples are available for re-testing.
6. Design a randomized clinical trial to assess the clinical benefit of olaparib in the heavily-pretreated gBRCAm ovarian cancer population. You may wish to design a study using an "investigator's choice" as a control arm.

Please request a response by 4 PM Friday, 7/18.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730

Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
07/07/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CLinPharm comments to AZ"s June 18 Response to IR
Date: Tuesday, June 24, 2014 7:39:07 AM
Attachments: image005.png
image006.png

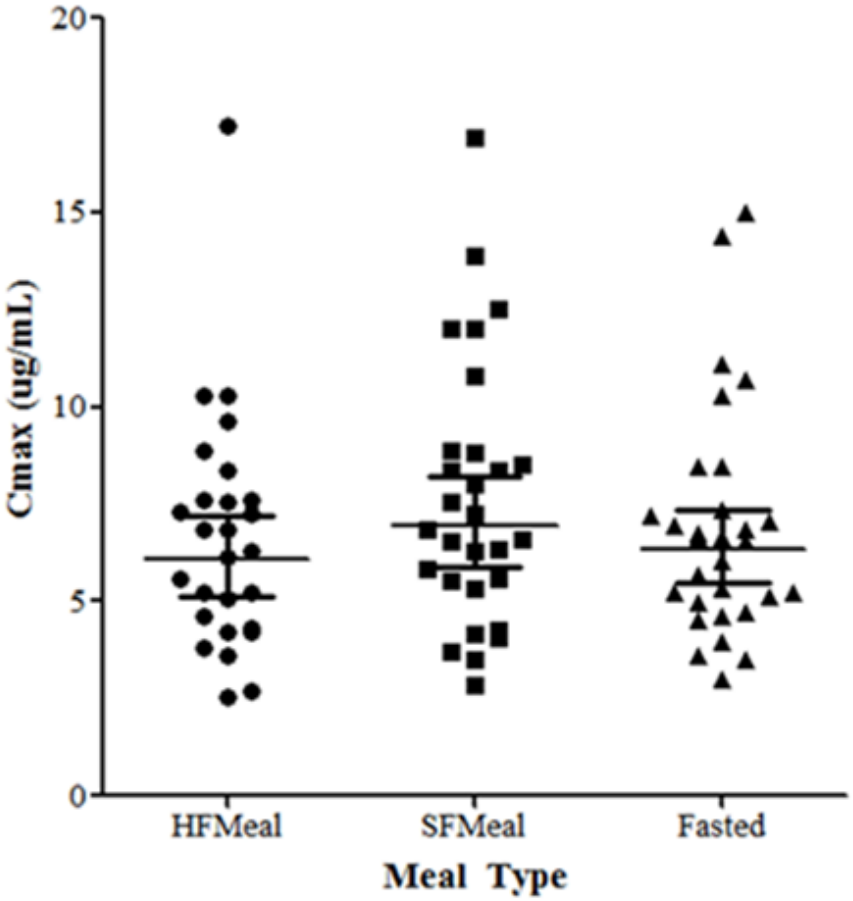
Hi Darci,

The following are FDA responses provided by our Clin Pharm team. Please respond accordingly **by 4 PM Monday June 30**:

Please see our response to your comments sent on June 18th in response to our comments sent on June 16th

1. AstraZeneca acknowledges that Trial D081AC00001 showed a small average effect of food on AUC (20% increase); however approximately 20% of patients showed a 50% or greater increase in AUC and approximately 10% of patients had a 70% or greater increase in exposure. Given the known variability in PK following dosing with the olaparib capsule formulation, which is likely to increase (b) (4) and the lack of tolerability data from patients exposed to olaparib (b) (4), AstraZeneca considers it in the best interest of the patient to provide some guidance (b) (4). (b) (4)

   FDA Response: From your submitted data we have not been able to conclude that food has a significant effect on the bioavailability of the olaparib capsules. Although some patients showed a 50% or greater increase in olaparib AUC while dosing with food, we cannot rule out the possibility that this is due to between occasion variability. Considering that PK variability has been observed in all your trials and between occasion variability cannot be ruled out, we continue to recommend that consideration should be given to improving patient convenience and potentially compliance and tolerability.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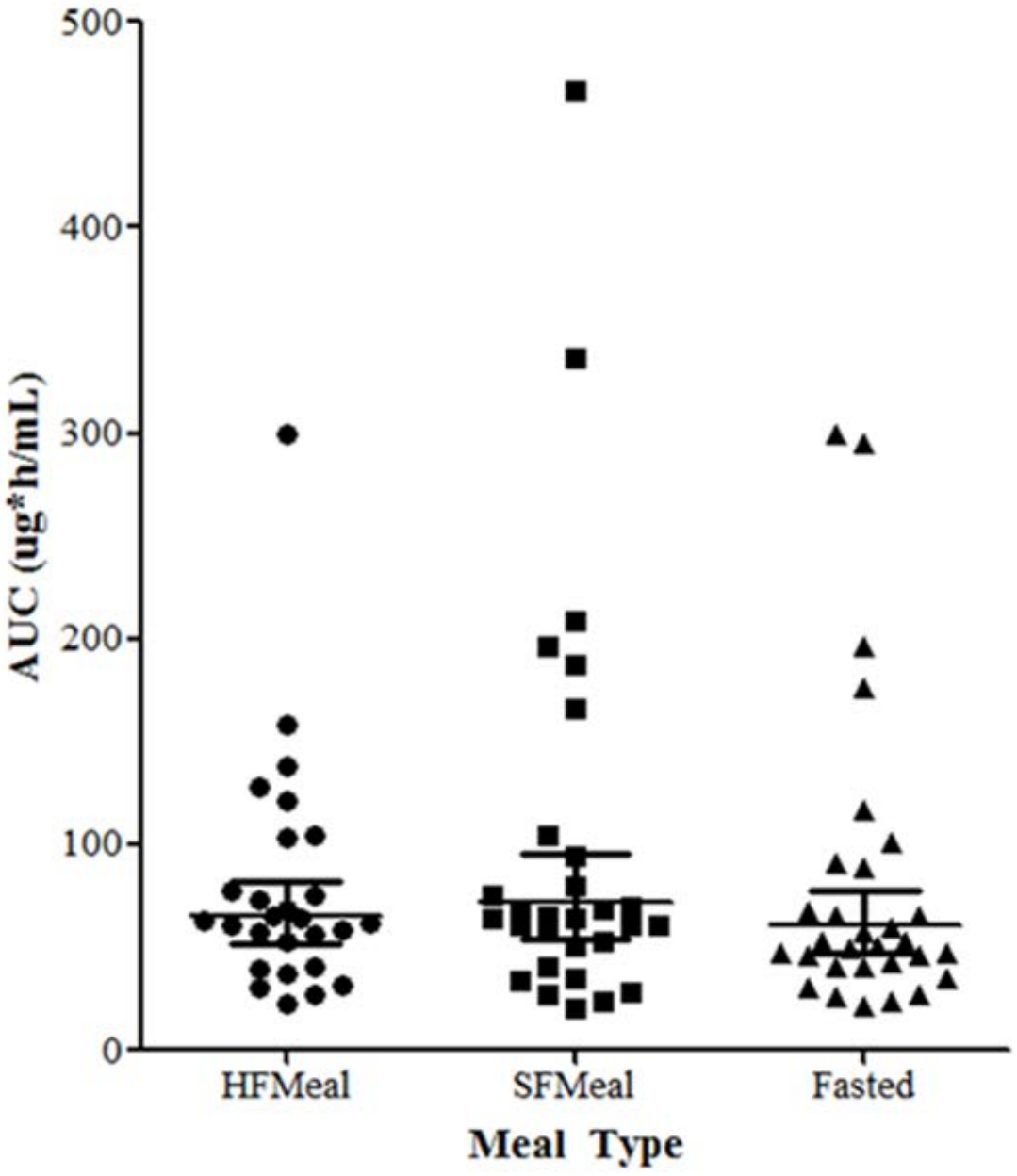

2. The effect of food on the tablet formulation is different to the capsule- the tmax is delayed by 2.5 h and Cmax is reduced (stat sig reduction of 21% (TR = 0.79 with a 90% CI from 0.72 to 0.86)), but there was little impact on AUC (TR = 1.08; 90% CI 1.01 to 1.16). A preliminary analysis of the effect of a light snack on the pharmacokinetics of olaparib tablets has been investigated in study D0810C00024, and the data suggest that the intake of a light snack does not impact the pharmacokinetics (PK) of olaparib. Anecdotally, investigators reported that this helped GI tolerability, although this could not be verified from the AE reports. In the phase III studies, which use the tablet formulation, patients are allowed to take olaparib tablets with a light snack. However, no such data exists for the capsule formulation.

   FDA Response: This information is helpful. It appears both the capsule and tablet formulation do not have a significant food effect (b) (4)

[redacted] (b) (4).

3. AstraZeneca agrees that the information provided to the prescriber and patient must be clear and helpful, and looks forwards to working with the Agency to agree appropriate wording around dosing capsules [redacted] (b) (4). If acceptable by the Agency, [redacted] (b) (4) and that it is recommended that [redacted] (b) (4).

   FDA Response: Please see our response above. As we do not usually add data to the dosage and administration section, we recommend either not stating anything regarding food or stating that it may be taken without regards to food. The data can be included in Section 12 of the label. We look forward to working with you on labeling.

Please also consider how to utilize the food effect information to improve the design of your ongoing phase 3 trial.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
06/24/2014

From:	Venugopal, Rajesh
To:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Cc:	Debbie.Mackenzie@astrazeneca.com; darci.bertelsen@astrazeneca.com
Subject:	NDA 206162 Olaparib - Clinical Pharmacology Information Request -- PBPK IR
Date:	Wednesday, June 18, 2014 10:58:47 AM

Hello Lori,

Our Clinical pharmacology team has the following information request that require your response:

On March 18, 2014, you agreed to submit updated PBPK study reports in late May/early June as part of the Day 120 update. The updated PBPK reports were to address comments provided to you on Mar 12, 2014, including comparison between model prediction and observed data from the ongoing drug interaction studies using strong CYP3A inhibitor itraconazole and strong CYP3A inducer rifampin, and necessary modification of the initial olaparib PBPK model.

1. Based on the observed magnitude of the effect of strong CYP3A modulators on olaparib pharmacokinetics, you should also simulate the following scenarios and find a dose of olaparib in the presence of a moderate CYP3A inhibitor (e.g. 200 mg fluconazole once daily) or a moderate CYP3A inducer (e.g. 400 mg efavirenz once daily) that will match the exposure of 400 mg alone
2. Please explore the effect of dissolution in your olaparib PBPK model to describe potential PK nonlinearity at doses >100 mg.

Please provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .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. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

Please submit this information **by 4 PM Tuesday June 24, 2014**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
06/18/2014

From:	Venugopal, Rajesh
To:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Cc:	Debbie.Mackenzie@astrazeneca.com; darci.bertelsen@astrazeneca.com
Subject:	NDA 206162 (Olaparib) - ClinPharm Comment
Date:	Monday, June 16, 2014 3:44:17 PM

Hello Lori,

Our clin – pharm team has the following comment that require your response

Considering the results of Trial D081AC00001 which show a minimal effect of food on Cmax and AUC of olaparib, we recommend you consider the dosing of olaparib capsules (b) (4) . We currently have no data to support whether food would be able to assist in the GI tolerability of the olaparib capsules, although this approach has been used for other drugs.

Please respond to us with your thoughts or proposal **by 4 PM Wednesday 06/18/14**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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/s/

RAJESH VENUGOPAL
06/16/2014

From: Venugopal, Rajesh
To: Chlysta, Lori A
Cc: "Bertelsen, Darci L"; Debbie.Mackenzie@astrazeneca.com
Subject: RE: Olaparib NDA 206162: Teleconference regarding May 22, 2014 FDA IR
Date: Friday, June 13, 2014 2:07:02 PM

Hi Lori,

During our teleconference on May 28, 2014, it was decided that your group would provide us with datasets in the NONMEM format for Study 24 groups 1 and 6, including group variable identifiers in the dataset via email on June 13, 2014 (See item II below, last bullet highlighted). Can you confirm that you will be able to submit the datasets for study 24 by today?

rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, May 30, 2014 11:33 AM
To: Alebachew, Elleni; Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: Olaparib NDA 206162: Teleconference regarding May 22, 2014 FDA IR

Hi Elleni and Rajesh,

Below is the AstraZeneca understanding of the agreements made during the May 28, 2014, teleconference.

I. Data consistency check and further request on datasets "pk2safe.xpt" and "pkpfseff.xpt" submitted on May 9th, 2014.

As shown in the table below, the number of patients is not consistent among different submission datasets for Study D0810C00009 (Study 09) and Study D0810C00012 (Study 12). To be consistent with Table 12 of the CSRs of Studies 09 and 12, include all patients of these two studies to datasets "pk2safe.xpt" and "pkpfseff.xpt".

AstraZeneca Response: For studies 9 and 12 a number of patients (9 and 4 respectively) had PFS values but were missing dose time or concentration data. It was therefore not possible to determine PK in these patients. As a consequence these patients were not included in the datasets "pk2safe.xpt" and "pkpfseff.xpt". For further detail on each excluded patient please see the document "Data consistency check" (attached).

Based on "pkpfseff.xpt" submitted on 09 May 2014, the calculated median PFS levels are not consistent with the values reported in Table 8 in Clinical Overview for Studies 09 and 12.

AstraZeneca Response: As outlined above, a number of patients were not included in the pkpfseff.xpt file due to there being no PK data for those patients. Consequently, the number of subjects contributing data to the calculation of mean PFS is different in pkpfseff.xpt compared to the numbers of patients included in the calculation of the reported values in Table 8 of the Clinical Overview and we would therefore not expect the calculated values to

be the same.

Also, based on "adpfspc.xpt" submitted for Study 12, the calculated median PFS levels are not consistent with the values reported in Table 8 of Clinical Overview for Study 12. Please explain.

AstraZeneca Response: The calculated median PFS levels using adpfspc.xpt for Study 12 are based on central review of RECIST and are consistent with the values reported in Table 11.2.1.10 of the CSR for Study 12. Table 8 in the clinical overview presents the median PFS based on investigator assessment of RECIST.

Number of Patients Reported from Different Sources of NDA206162

	Table12, CSRs	pk1pool.xpt	pk1safe.xpt	pk2eff.xpt	pk2safe.xpt	pkpfseff.xpt
100 mg BID, Study 09	24	20	20	15	20	20
400 mg BID, Study 09	33	28	28	24	28	28
200 mg BID, Study 12	32	31	31	31	31	30
400 mg BID, Study 12	32	30	30	30	30	30
Submission Date	03-Feb-14	15-Apr-14	15-Apr-14	15-Apr-14	9-May-14	9-May-14

Include the following variables to datasets "pk2safe.xpt" and "pkpfseff.xpt", if available:

1. Time to disease progression in the penultimate platinum therapy prior to enrollment (preferably numeric value as opposed to categories)
2. BRCA mutation type (1 vs. 2)
3. Number of prior platinum chemotherapy regimens
4. Number of prior total chemotherapy regimens

and

5. All efficacy variables that are available by study design such as "RECIST ORR" and "Best Percentage Change in Tumor Size (%)" to dataset "pkpfseff.xpt"

Response I: May 28, 2014 Teleconference Agreements

- Response document outlining the apparent discrepancy in patient numbers to be provided via email on **May 29, 2014**. Attached
- Requested Datasets for studies 02, 08, 09, 12 and 24 with the additional variables, including observed C_{min}, where possible will be provided via email **June 4, 2014**.
- Official submission of response document and datasets will be submitted to NDA 206,162 on **June 6, 2014**.

II. New Dataset request for Study D0810C00024 (Study 24). Study 24 may help evaluate the exposure-safety/efficacy relationship of olaparib for a higher range of exposures due to

the higher bioavailability of the tablet and the [redacted] (b) (4) regimen. For Study 24, construct an analysis dataset including the following items if available:

1. Unique Subject Identifier (USUBJID) and all demographic variables that are available
2. 20 patients in Group 1, and the 60 patients in Group 8
3. Time to disease progression in the penultimate platinum therapy prior to enrollment (preferably numeric value as opposed to categories)
4. BRCA mutation type (1 vs. 2)
5. Number of prior platinum chemotherapy regimens
6. Number of prior total chemotherapy regimens
7. All efficacy variables that are available by study design
8. All adverse event variables including Anemia, Grade 1 Anemia, Grade 2 Anemia, Grade 3-5 Anemia, Thrombocytopenia, Grade 1 Thrombocytopenia, Grade 2 Thrombocytopenia, Grade 3-5 Thrombocytopenia, Neutropenia, Grade 1 Neutropenia, Grade 2 Neutropenia, Grade 3-5 Neutropenia, Leukopenia, Grade 1 Leukopenia, Grade 2 Leukopenia, Grade 3-5 Leukopenia, Lymphopenia, Grade 1 Lymphopenia, Grade 2 Lymphopenia, Grade 3-5 Lymphopenia, Grade 3-5 nausea
9. PK information including Formulation, Treatment (Dose and Frequency), Steady State AUC of Olaparib, Pre-dose Olaparib Concentration at Steady State (Cmin_ss_obs), Predicted Steady State Trough Concentration of Olaparib (Cmin_ss_pred), Steady State Peak Concentration of Olaparib, Observed Steady State Trough Concentration, or Observed Cmax at Steady State, Apparent Clearance, Dose Reduction (Yes or No), Final Dose, Final Frequency, Duration Per Each Actual Treatment, if available

Response II: May 28, 2014 Teleconference Agreements

- Group 8 data is not currently available and could not be provided before the end of June 2014. Since the two dose levels delivering the highest exposures are the 300 mg bd and the 400 mg bd tablet continuous schedules, those would seem to be the most appropriate dose groups to include in the planned analyses of exposure-AE relationships. Both those dose levels were administered to patients in Group 6
- Data specification document to confirm the contents of the data set will be provided via email no later than **June 6, 2014**, in advance of the datasets. In addition, identification of the group will be added as a variable.
- Requested datasets for study 24 will include additional variables, where possible.
- Datasets in the NONMEM format for Study 24 groups 1 and 6, including group variable identifiers in the dataset via email on **June 13, 2014**.

III. Assess the within-study dose proportionality for studies 02, 07, 09, and 12

Response III: May 28, 2014 Teleconference Agreements

- Statistical analyses of dose proportionality (following single dosing and following multiple dosing) will be conducted within each individual study for Studies 01 and 02 (based on NCA derived C_{max} and AUC values)
- In separate statistical analyses, dose proportionality will be assessed based upon population PK based C_{max} and AUC estimates for Studies 07, 09 and 12 and, if

possible also conducted on observed C_{min} values from these studies

- Method of assessment:
  - linear regression of log-transformed AUC and Cmax on log(dose) adjusted by subject
  - ANOVA dose normalized AUC and Cmax values with effects for subject and trial day.
- Dose proportionality analysis for Studies 01, 02, 09 and 12 will be provided via email on **June 6, 2014**.
- Dose proportionality analysis for Study 07 will be provided via email on **June 13, 2014**.

Below is the complete list of AstraZeneca participants.
Helen Swaisland (Clinical Pharmacologist)
Helen Mann (Global Product Statistician)
Mark Reynolds (Programming Team Leader)
Paul Frost (Programmer)
Marc-Antoine Fabre (Pharmacomatrician)
Anitra Fielding (Medical Science Director)
Jane Robertson (Executive Global Clinical Director)
Angela Race (Clinical Information Manager)
Debbie Mackenzie (Global Regulatory Affairs Director)
Darci Bertelsen (US Regulatory Affairs Director)

As always, if you have any questions, please don't hesitate to contact me.

Darci

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From: Alebachew, Elleni [mailto:Elleni.Alebachew@fda.hhs.gov]
Sent: Wednesday, May 28, 2014 12:55 PM
To: Bertelsen, Darci L
Cc: Venugopal, Rajesh
Subject: RE: Olaparib NDA 206162: Teleconference regarding May 22, 2014 FDA IR

Hi Darci,

Please email me an updated list of attendees. Also, could you please email me AZ's understanding of what is requested as well as the due dates AZ committed to deliver.

Thanks,

Elleni

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Wednesday, May 28, 2014 10:19 AM
To: Venugopal, Rajesh; Alebachew, Elleni
Cc: Chlysta, Lori A
Subject: Olaparib NDA 206162: Teleconference regarding May 22, 2014 FDA IR

Rajesh and Elleni,

Below are a list of questions/clarifications AstraZeneca would like to cover at today's teleconference scheduled for 12:00 p.m.

Request I

AstraZeneca understands the need to provide the requested information as quickly as possible. To that end, is it possible to submit the requested datasets via email and followed up with a submission to the NDA via eCTD at a later date, or must they only be submitted via eCTD?

Request II

For the datasets requested for Study 24, it is our interpretation that datasets are needed for Group 1 and 8 and that data for group 6 is not required. Is that an accurate interpretation?

Request III

Please could the Division clarify:
-Is the Division requesting a statistical analysis of dose proportionality within each individual study?
-Could the Division confirm the parameters for the statistical analysis would be AUC and C_{max}
-Could the Division confirm the method of assessment :

(1) using linear regression of log-transformed AUC and C_{max} on log(dose) adjusted by subject

(2) using ANOVA dose normalized AUC and C_{max} values with effects for subject and trial day.

The AstraZeneca attendees will be:

Helen Swaisland (Clinical Pharmacologist)
Helen Mann (Global Product Statistician)
Mark Reynolds (Programming Team Leader)
Marc-Antoine Fabre (Pharmacomatrician)
Anitra Fielding (Medical Science Director)
Angela Race (Clinical Information Manager)

Debbie Mackenzie (Global Regulatory Affairs Director)
Darci Bertelsen (US Regulatory Affairs Director)

Lastly, as a reminder, the call-in numbers are:

(b) (4)

Darci Bertelsen
US Regulatory Affairs Director

AstraZeneca
GRA | US Regulatory Affairs
C2C-717, 1800 Concord Pike, Wilmington DE, 19802
T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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RAJESH VENUGOPAL
06/13/2014

From:	Venugopal, Rajesh
To:	Chlysta, Lori A (lori.chlysta@astrazeneca.com)
Cc:	darci.bertelsen@astrazeneca.com; "Debbie.Mackenzie@astrazeneca.com"
Subject:	NDA 206162 Olaparib Clinical pharmacology Information Request
Date:	Thursday, June 12, 2014 3:54:53 PM

Hello Lori,

Our clin pharm team has the following information request requiring your response:

Please identify whether any of the PK data submitted to the NDA is from batches made at the commercial site. Please respond by noon on 06/13/14.

Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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RAJESH VENUGOPAL
06/12/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - Clinical Pharmacology Information Request
Date: Wednesday, June 11, 2014 8:42:11 AM

Good Morning Darci,

Our clinical pharmacology team has the following requests requiring your response:

We have concerns about the variability in the observed PK data including a likelihood of batch to batch variability and differences in PK observed across the trials. In addition it is not clear if olaparib truly has less than dose proportional increases in exposure as stated in your clin pharm summaries and in the proposed label. This concern is also raised by your responses to our IRs as shown below (1 and 2). Identify the PK data that would be most relevant and would reflect the exposures likely to be observed with the planned commercial product and that used in Trial D0810C00019. Please also clarify whether you have any PK data on the capsule batches manufactured at the commercial site. You could use batch dissolution data and other supportive evidence in order to support the selection of PK data and conclusions to include in the label.

1. *Report on Dose Proportionality sent via email on 06/06/14 – Your conclusion was as follows, "There was some evidence to support dose proportionality seen in Studies D0810C00001 (single bd dose), D0810C00002 (single od and multiple od doses) and D0810C00007 (multiple bd doses) but only limited evidence was seen from Studies D0810C00001 (multiple bd doses), D0810C00002 (single and multiple bd doses), D0810C00009 (multiple bd doses), and D0810C00012 (multiple bd doses)."*

2. *The following was sent in your response to our IR on 04/25/14: "All batches used during the period that PK sampling was being performed in Study 02 and Study 07 were manufactured at the development site and demonstrated satisfactory release based on* (b) (4) *. Since there were other potential explanations for the difference seen between the studies eg, different patient population (early disease versus advanced, heavily pre-treated patients), use of anaesthetics prior to collection of samples from Study 07 patients, confidence that fasting restrictions would have been adhered to in Study 07 (due to surgery) but not necessarily in Study 02 patients, no further investigation into the difference between the studies was conducted at that time. Subsequently, a more discriminatory polysorbate dissolution method has been developed which shows some variability in dissolution profiles between capsule batches manufactured at the development site(see Question 95). Studies 02 and 07 were dosed with different batches of capsules. Patients in the 100,200 and 400 mg cohorts in Study 07 were dosed with a batch now known to showslower dissolution in the polysorbate test. However for the majority of patients in Study 02 no retrospective polysorbate dissolution data are available. Based on the information given in the response to Question 95 it is acknowledged that dissolution performance could be a contributing factor to the bioavailability differences (up to16%) between Studies 02 and 07; but due to limited polysorbate data it is not possible to determine the extent of this potential contribution compared to the other possible factors described above."*

Please respond **by 4 PM Monday June 16**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
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RAJESH VENUGOPAL
06/11/2014

From:	Venugopal, Rajesh
To:	"Bertelsen, Darci L"
Cc:	Chlysta, Lori A
Subject:	RE: NDA 206162 (Olaparib) - CMC information Request
Date:	Monday, June 09, 2014 10:03:13 AM

Hi Darci,

According to the DMF folks at our Agency, I've been told that the LOA was not officially submitted to DMF (b) (4) at the FDA. Would you please advise the DMF holder that they need to submit the LOA to the Agency as soon as possible?
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, June 09, 2014 9:17 AM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) - CMC information Request

Hi Rajesh,

I hit send too soon.

The requested DMF is attached. It was our understanding that this was submitted to FDA by the DMF holder previously.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Monday, June 09, 2014 8:47 AM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) - CMC information Request

Hello Darci,

Our CMC teams has the following urgent request:

The CMC team would like a status on the Letter of Authorization for Type IV DMF (b) (4) ((b) (4)), the excipient. The CMC folks have been expecting it since April 2014.

As of this morning, it has not been submitted by the DMF holder ((b) (4)) to the DMF (b) (4) and it has not been submitted by AZ to the NDA. I have been told that both of these things need to happen before the CMC team can review the DMF in support of the NDA.

Could you please provide this **as soon as possible**? They have been waiting for it since your commitment to provide it, back on 25-April-2014.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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RAJESH VENUGOPAL
06/09/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CMC information Request
Date: Monday, June 09, 2014 8:47:00 AM

Hello Darci,

Our CMC teams has the following urgent request:

The CMC team would like a status on the Letter of Authorization for Type IV DMF (b) (4) ((b) (4)), the excipient. The CMC folks have been expecting it since April 2014.
As of this morning, it has not been submitted by the DMF holder ((b) (4)) to the DMF (b) (4) and it has not been submitted by AZ to the NDA. I have been told that both of these things need to happen before the CMC team can review the DMF in support of the NDA.

Could you please provide this **as soon as possible**? They have been waiting for it since your commitment to provide it, back on 25-April-2014.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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RAJESH VENUGOPAL
06/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

METHODS VALIDATION
MATERIALS RECEIVED

AstraZeneca
Attention: Lori Chlysta
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Lori Chlysta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Olaparib capsule, 50 mg and to our March 12, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on June 5, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

MID-CYCLE COMMUNICATION

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for olaparib, 50 mg capsules.

We also refer to the teleconference between representatives of your firm and the FDA on May 14, 2014. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

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

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

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: Wednesday, May 14, 2014/2:00 PM
Application Number: NDA 206162
Product Name: Olaparib
Indication: Ovarian Cancer
Applicant Name: AstraZeneca

Meeting Chair: Amy McKee, MD
Meeting Recorder: Rajesh Venugopal, MPH, MBA

FDA ATTENDEES

Amna Ibrahim, MD, Acting Director, DOP1
Amy McKee, MD, Clinical Team Leader, DOP1
Geoffrey Kim, MD, Clinical Reviewer, DOP1
Gwynn Ison, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Statistics Team Leader, DBV
Gaetan Ladouceur, PhD, CMC Reviewer, ONDQA
Anne Marie Russell, PhD, CMC Reviewer, ONDQA
Okpo Eradiri, PhD, Biopharmaceutics Reviewer, ONDQA
Ali Al Hakim, PhD, CMC Branch Chief, ONDQA
Elimika Pfuma, PharmD, PhD, Clinical Pharmacology Reviewer, DCP V
Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP V
Brian Booth, PhD, Deputy Director, Clinical Pharmacology, DCP V
Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1
Christy Cottrell, Chief, Project Management Staff, DOP1

APPLICANT ATTENDEES

Jane Robertson, MB BS, MD, Executive Global Clinical Director
Helen Swaisland, BSc, Principal Clinical Pharmacology Scientist
Debbie Mackenzie, BSc, MSc, Global Regulatory Leader
Darci Bertelsen, BA, US Regulatory Affairs Director
Hesham Abdullah, MD, MSc, RAC, VP, Global Regulatory Affairs, Oncology
Antoine Yver MD MSc, VP, Global Medicines Development Head, Oncology and New Opportunities
Tony Ho, MD, Global Product Vice President Olaparib, Oncology
Miles Dunn, MA, Global Programming Lead, Olaparib
Marc-Antoine Fabre, Sr. Pharmacometrician
Roy Jamieson, BPharm, Regulatory CMC Director
Helen Mann, MSc, Global Product Statistician
Jim Murray, BSc, PhD, Project Director, Pharmaceutical Development
Andrew Stone, BSc, MSc, Biometrics & Information Science TA Head Oncology

Eveline Wesby-van Swaay, MD, VP, Oncology Head, Global Medicines Development

EASTERN RESEARCH GROUP ATTENDEES
(b) (6), Independent Assessor

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Chemistry, Manufacturing and Controls (CMC)

Drug Substance:

The amendment received on April 15, 2014, is under review. Any further new information requests from the Agency will be sent separately.

Drug Product:

1. The proposed acceptance criteria (release and stability) for % (b) (4) is under review. Bioavailability and stability data have been requested by the Agency.

2. The proposed (b) (4) analytical method for % (b) (4) is under review. Additional information has been requested regarding robustness and other characteristics of the method.

3. The proposed controls for the excipient Lauroyl polyoxyl-32 glycerides (LMG) are under review. The Agency awaits submission of a Letter of Authorization (LOA) to DMF (b) (4) for (b) (4) to be supplied by (b) (4) as promised in the response to our Information Request of April 14, 2014. The Agency notes that this LOA needs to be submitted to the DMF and the NDA.

4. The proposed shelf life is under review. Additional data have been requested of the applicant.

Clinical/Statistical Efficacy

1. Reproducibility of the magnitude of effect seen in Study 19:

a. The PFS analysis of the gBRCAm population did not have pre-specified alpha allocation; therefore, it is still being reviewed on how to handle the p-values.

b. There is concern that the retrospective identification of the gBRCAm population resulted in imbalances of known prognostic factors between the study arms.

c. The wtBRCA placebo population appeared to have equal if not slightly longer PFS intervals as compared to the gBRCAm placebo population. There is concern that the gBRCAm placebo population may have "underperformed" and that the PFS duration of the placebo-treated arm may be longer in the SOLO-2 trial, thus attenuating the magnitude of effect demonstrated in the olaparib arm.

d. There are concerns regarding the different formulation used in the confirmatory trial, SOLO-2. The new tablet formulation is not bioequivalent to the capsule formulation, and a different dose with different exposure will be used in the confirmatory trial. Whether the exposure, which presumably will be higher in the confirmatory trial, will affect efficacy and safety is unknown at this time.

2. Data integrity of Study 19:

a. Many of these issues have been addressed in the responses to Information Requests.

b. Recent responses to Information Requests are being reviewed by the clinical/OSI team.

Clinical/Safety

3. MDS/AML

a. The Agency is awaiting a response to Information Request that will be submitted on May 15, 2014, with an update on the incidence and characteristics of MDS/AML in the olaparib safety database.

4. 4 month safety update

a. The Agency is awaiting submission for review.

Clinical/Device

1. There are concerns regarding the feasibility of the potential simultaneous co-approval of drug and companion diagnostic based on the newly proposed PMA submission timeline by the device manufacturer.

Reference ID: 3519600

3.0 INFORMATION REQUESTS

Any further new information requests will be sent separately.

Biopharmaceutics (IR Comments sent to Applicant on May 12, 2014)

i) Individual vessel release dissolution data for 17 clinical batches.

ii) Lack of effect of [redacted] (b) (4) on bioavailability of proposed product not supported by data provided to date by applicant.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Agency does not think that a Risk Evaluation and Mitigation Strategy will be necessary.

5.0 ADVISORY COMMITTEE MEETING

As communicated to you in the Filing Communication Letter dated April 3, 2014, an Oncologic Drugs Advisory Committee Meeting is planned for June 25, 2014.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Advisory Committee Meeting	June 25, 2014
Late-Cycle Meeting	August 29, 2014
PDUFA Action Date	October 3, 2014

Reference ID: 3519600

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/s/

RAJESH VENUGOPAL
06/05/2014

AMY E MCKEE
06/05/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - Clinical Pharmacology Information Request
Date: Wednesday, June 04, 2014 10:51:55 AM

Hi Darci,

1. Please refer to the information request sent on 04/18/14 (added below) and your response. The response does not appear to address the location of the PK Parameters (such as Cmax, AUC, T1/2, Cl etc) for the total radioactivity including the datasets and a summary as they are not discussed in the study report. **Please address the IR in full by 4 PM Friday 06/13/14**.

   April 18, 2014 Information Request:
   Our clinical pharmacology team have the following requests that require team's response:
   1. For the ADME trial D0810C00010, please provide the location of the datasets that include individual and mean plasma and whole blood PK concentrations and parameters for total radioactivity in the edr. We note that the study report only includes information about the mean Cmax and Tmax of total radioactivity. Please submit a summary of other PK parameters for the total radioactivity as done for the olaparib moiety.
   ***Please respond by COB on April 25th, 2014**.*

   AstraZeneca Response: The individual plasma and whole blood PK concentration data for study 10 is in the SDTM.PC domain that was sent to FDA on March 26, 2014 (Sequence 0004). The file names are as follows:
   Individual Plasma PK concentration is PC.PCTESTCD=OLAP14C and PC.PCSPEC=PLASMA.
   Individual whole blood PK concentration is PC.PCTESTCD=OLAP14C and PC.PCSPEC=BLOOD.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
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Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
06/04/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (olaparib) IRT/QT Information Request
Date: Wednesday, June 04, 2014 9:31:18 AM

Hello Darci,

Please refer to item 3 (shown below) of the information request sent to you on 02/10/14 regarding the Day 120 submission for QT/IRT review. Please clarify whether all the components(including the datasets for the interim data and related ECGs) have been submitted. If they have not been submitted, please submit into the edr **by 4 PM Monday 06/09/14**.

3. When you submit your 'QT study' report, please include the following items:
a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
b. Electronic copy of the study report
c. Electronic or hard copy of the clinical protocol
d. Electronic or hard copy of the Investigator's Brochure e. Annotated CRF
f. A data definition file which describes the contents of the electronic data sets
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure response analyses
h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any:
i. Deaths
ii. Serious adverse events
iii. Episodes of ventricular tachycardia or fibrillation
iv. Episodes of syncope
v. Episodes of seizure
vi. Adverse events resulting in the subject discontinuing from the study
k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
l. A completed Highlights of Clinical Pharmacology Table

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA

Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
06/04/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - Clincial Information Request
Date: Friday, May 30, 2014 11:55:44 AM

Hello Darci,

Our Clinical team has the following information request that require your response. We request that you confirm (or fill in, where missing) the germline BRCA (gBRCA) mutation status for the patients in the list below:

gBRCA mutation status for MDS cases:

1. Study 19, E0805002- gBRCA unknown
2. Study 19, E1801002- gBRCA wildtype
3. Study 19, E0801001- gBRCA mutated
4. Study 19, E1808004- gBRCA mutated
5. Study 41, E1405004-
6. Study 41, E1503001-
7. Study 12, E7001010- gBRCA mutated
8. Study 12- E6007014- gBRCA mutated
9. Study 12- E8001092- (Doxil)- gBRCA mutated
10. Study 42, E0302009- gBRCA mutated (myriad)
11. Study 42- E4007006-
12. Study 42- E4003003-
13. Study 42- E7802003- gBRCA mutated (myriad)
14. Study 42- E7802029- gBRCA mutated (myriad)
15. Study 42- E4001012-
16. Study 9- E0017011- gBRCA mutated (myriad)
17. Study 9- E0613008-
18. Study 2- 001-0078-
19. Study 4- 003-2117-
20. Study 98- E8348038-
21. Study 59- 0810C00059/008-
22. Study 24- E0008004-

23. INV- D0810C0055/JH001-

24. INV- D081C0055/JH004-

Please respond **by 4 PM Monday, June 2.**

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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/s/

RAJESH VENUGOPAL
05/30/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) Response to CMC comments required
Date: Thursday, May 29, 2014 4:50:55 PM

Hello Darci,

Our CMC team has the following comments requiring your response:

Your response of 23-May-2014 has been reviewed and is not acceptable. We reiterate our previous comment:

1. **Analytical Methods:** As submitted, all regulatory analytical method procedures for quality control of the commercial drug substance and drug product follow the format: Principle, Procedure and Exemplified Method. This format is too broad and insufficiently specific to serve as the regulatory method procedure for this NDA.
    a. Revise the procedures to describe only the specific analytical procedure proposed for the regulatory method.
    b. Remove the use of "for example" and "exemplify the operation of the method"
    c. Remove the Principle, Procedure and Exemplified Method sections and instead incorporate the specific information (not general) into the description of the analytical procedure.
    d. Remove any remaining general descriptions and replace them with the specific procedure used (e.g HPLC column type, wavelength, solution, etc.)
    e. Remove the Appendix describing adjustments to the exemplified method detail, which is considered an unacceptable Comparability Protocol.

Provide a response by **4 PM Friday, 6-Jun-2014**.

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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/s/

RAJESH VENUGOPAL
05/29/2014

From: Alebachew, Elleni
To: Bertelsen, Darci L (darci.bertelsen@astrazeneca.com)
Cc: Venugopal, Rajesh
Bcc: Li, Hongshan
Subject: NDA 206162- Information Request
Date: Thursday, May 22, 2014 4:11:00 PM
Importance: High

Hello,

We have the following information requests for olaparib (NDA206162). Respond to the request I within 3 business days, request II within 5 business days, request III within 7 business days.

I. Data consistency check and further request on datasets "pk2safe.xpt" and "pkpfseff.xpt" submitted on May 9th, 2014.

As shown in the table below, the number of patients is not consistent among different submission datasets for Study D0810C00009 (Study 09) and Study D0810C00012 (Study 12). To be consistent with Table 12 of the CSRs of Studies 09 and 12, include all patients of these two studies to datasets "pk2safe.xpt" and "pkpfseff.xpt". Based on "pkpfseff.xpt" submitted on 09 May 2014, the calculated median PFS levels are not consistent with the values reported in Table 8 in Clinical Overview for Studies 09 and 12.

Also, based on "adpfspc.xpt" submitted for Study 12, the calculated median PFS levels are not consistent with the values reported in Table 8 of Clinical Overview for Study 12. Please explain.

Number of Patients Reported from Different Sources of NDA206162						
	Table12, CSRs	pk1pool.xpt	pk1safe.xpt	pk2eff.xpt	pk2safe.xpt	pkpfseff.xpt
100 mg BID, Study 09	24	20	20	15	20	20
400 mg BID, Study 09	33	28	28	24	28	28
200 mg BID, Study 12	32	31	31	31	31	30
400 mg BID, Study 12	32	30	30	30	30	30
Submission Date	03-Feb-14	15-Apr-14	15-Apr-14	15-Apr-14	9-May-14	9-May-14

Include the following variables to datasets "pk2safe.xpt" and "pkpfseff.xpt", if available:

1. Time to disease progression in the penultimate platinum therapy prior to enrollment (preferably numeric value as opposed to categories)
2. BRCA mutation type (1 vs. 2)
3. Number of prior platinum chemotherapy regimens
4. Number of prior total chemotherapy regimens

and

5. All efficacy variables that are available by study design such as "RECIST ORR" and "Best Percentage Change in Tumor Size (%)" to dataset "pkpfseff.xpt"

Please respond to item number I by COB May 28, 2014

II. New Dataset request for Study D0810C00024 (Study 24). Study 24 may help evaluate the exposure-safety/efficacy relationship of olaparib fora higher range of exposures due to the higher bioavailability of the tablet and the [redacted] (b) (4) regimen. For Study 24, construct an analysis dataset including the following items if available:

1. Unique Subject Identifier (USUBJID) and all demographic variables that are available
2. 20 patients in Group 1, and the 60 patients in Group 8
3. Time to disease progression in the penultimate platinum therapy prior to enrollment (preferably numeric value as opposed to categories)
4. BRCA mutation type (1 vs. 2)
5. Number of prior platinum chemotherapy regimens
6. Number of prior total chemotherapy regimens
7. All efficacy variables that are available by study design
8. All adverse event variables including Anemia, Grade 1 Anemia, Grade 2 Anemia, Grade 3-5 Anemia, Thrombocytopenia, Grade 1 Thrombocytopenia, Grade 2 Thrombocytopenia, Grade 3-5 Thrombocytopenia, Neutropenia, Grade 1 Neutropenia, Grade 2 Neutropenia, Grade 3-5 Neutropenia, Leukopenia, Grade 1 Leukopenia, Grade 2 Leukopenia, Grade 3-5 Leukopenia, Lymphopenia, Grade 1 Lymphopenia, Grade 2 Lymphopenia, Grade 3-5 Lymphopenia, Grade 3-5 nausea
9. PK information including Formulation, Treatment (Dose and Frequency), Steady State AUC of Olaparib, Pre-dose Olaparib Concentration at Steady State (Cmin_ss_obs), Predicted Steady State Trough Concentration of Olaparib (Cmin_ss_pred), Steady State Peak Concentration of Olaparib, Observed Steady State Trough Concentration, or Observed Cmax at Steady State, Apparent Clearance, Dose Reduction (Yes or No), Final Dose, Final Frequency, Duration Per Each Actual Treatment, if available

Please respond to item number II by COB May 30, 2014

III. Assess the within-study dose proportionality for studies 02, 07, 09, and 12

Please respond to item number II by COB June 2, 2014

Regards,

Elleni Alebachew, MS, RAC
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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E-mail: Elleni.Alebachew@fda.hhs.gov
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/s/

ELLENI K ALEBACHEW
05/23/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

PROPRIETARY NAME REQUEST WITHDRAWN

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

ATTENTION: Darci L. Bertelsen
Director, Regulatory Affairs

Dear Ms. Bertelsen:

Please refer to your New Drug Application (NDA) dated February 3, 2014, received February 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Olaparib Capsules, 50 mg.

We also refer to:

- Your correspondence dated and received on February 19, 2014, requesting review of your proposed proprietary name, (b) (4)
- Your correspondence dated and received on May 5, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4), and the alternate name, (b) (4).

This proprietary name request for both names is considered withdrawn as of May 5, 2014.

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
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

FRANCES G FAHNBULLEH
05/15/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CMC and Biopharm Information Request
Date: Monday, May 12, 2014 4:09:46 PM

Hello Darci,

Our CMC and biopharmaceutics review team have the following information request that require your response on specific dates highlighted in red:

Chemistry and Manufacturing Controls (CMC):

1. **Analytical Methods:** As submitted, all regulatory analytical method procedures for quality control of the commercial drug substance and drug product follow the format: Principle, Procedure and Exemplified Method. This format is too broad and insufficiently specific to serve as the regulatory method procedure for this NDA.
    a. Revise the procedures to describe only the specific analytical procedure proposed for the regulatory method.
    b. Remove the use of "for example" and "exemplify the operation of the method"
    c. Remove the Principle, Procedure and Exemplified Method sections and instead incorporate the specific information (not general) into the description of the analytical procedure.
    d. Remove any remaining general descriptions and replace them with the specific procedure used (e.g HPLC column type, wavelength, solution, etc.)
    e. Remove the Appendix describing adjustments to the exemplified method detail, which is considered an unacceptable Comparability Protocol.
    f. **Submit revised procedures no later than 26-May-2014**.

2. **Drug product expiry**:
    a. Provide release and stability data for the attribute of % (b) (4), measured using the proposed commercial analytical method, for olaparib capsule registration batches and for the clinical batches administered in the pivotal clinical trial.
    b. For the clinical product (50 mg olaparib capsule), provide the age (months) at the time of administration to the clinical patients in the pivotal trial (Study 19).
        i. These data may be provided in excel files with tables listing the lot number, manufacture date, patient, date of administration, age of capsule, number of capsules.
        ii. It may be possible to consider all the capsules in a single bottle (approximately 500), which were distributed monthly, to be the average age of the capsules at time of distribution, provided this does not introduce any estimate error exceeding one month.
        iii. According to our estimate, this data set will include approximately 8 product lots in (b) (4) bottles administered to 136 patients from August 2008 to June 2010.
        iv. Do not include lots manufactured after the data cutoff date of June 30, 2010.
        v. Include a histogram of the number of capsules versus age of capsule at time of administration (bin size 1 month, mean, median, standard

deviation, etc.) for each lot.

vi. Include a histogram of all capsules administered to all patients receiving olaparib.

vii. Include a histogram of all capsules administered to all gBRCAm population patients receiving olaparib.

c. **Submit the requested information no later than 2-June-2014**.

The Agency recognizes that the requested information is extensive but considers that it may be necessary to address drug product shelf life issues regarding [redacted] (b) (4).

3. [redacted] (b) (4) in drug product:

a. Demonstrate robustness of the [redacted] (b) (4) to variations in the capsule properties of the commercial product. For example, some concerns regarding robustness of the method when used with the commercial product are:

i. Materials: Variations in the spectra can arise from different material suppliers:

The capsule used to prepare the calibration and validation sample sets in the [redacted] (b) (4) validation report was Size [redacted] (b) (4) supplied by [redacted] (b) (4). The calibration set was prepared using a different lot but the same supplier as the validation sample set. The capsules described in the drug product section (P.1) for the commercial product was USP grade hypromellose capsule shell from no specified supplier.

Material suppliers for the commercial product are not specified and therefore may vary. However, the material used to prepare the samples used to validate the method were each supplied by only a single source. Since the method must be demonstrated as sufficiently robust to provide valid measurements for the proposed commercial product, either provide data to demonstrate robustness from various suppliers, restrict the commercial product manufacturing to the materials used in the validation of the method or provide an alternate resolution to this issue.

ii. Printing: There is no mention of any printing on the validation and calibration sample sets. The commercial product is described as marked with "OLAPARIB 50 mg" and the AstraZeneca logo printed in black ink. Variations in spectra can arise from variations in the position of capsule printed area during data collection. The submitted analytical method does not specify the orientation of the capsule printed area during data collection.

iii. [redacted] (b) (4)

b. Demonstrate specificity to [(b) (4)].
   i. Provide data for [(b) (4)]% [(b) (4)] samples labeled on one plot. Data should include pretreated spectra in the analysis range.
   ii. Provide the [(b) (4)] beta coefficient and compare it to [(b) (4)] used in the model.

c. Describe the procedure employed and provide the data used to verify the % content of API [(b) (4)] in the drug product capsules used to validate the [(b) (4)] model for drug product [(b) (4)] analysis (Set 1, Set 2 and Set 3). The Method Validation (3.2.P.5.3) describes the olaparib 50 mg capsules as manufactured from [(b) (4)] (tested by XRD). It does not provide any description of testing of these capsules or data collected to confirm that this manufacturing process produced the intended mixture (i.e. [(b) (4)]).

d. **Submit the requested information no later than 26-May-2014**.

Biopharmaceuticals:

4. **Dissolution:** Submit the individual vessel dissolution data with descriptive statistics for each of the 17 batches, at release, used in study D0810C00019 (60227E08, 3075510R, 3070200R, 3071641R, 3072918R, 3065254R,3065255R, 3070199R, 3080106R, 3080721R, 3084949R, 3086689R, 3086691R,3090870R, 3091601R, 3094511R, 3094512R). Provide in tabular form, their respective dates of manufacture and duration of use in the Phase II study; include the dissolution test method used in release testing of each batch unless the same proposed regulatory method was used to test all 17 clinical batches. Similar to the stability data submitted earlier, please provide the dissolution data in excel format. **Submit the requested information no later than 26-May-2014**.

5. **Bioavailability:**
   a. FDA acknowledges your assurance that additional experimental work will be conducted to obtain a comprehensive understanding of [(b) (4)] in the drug product. However, your assertion that up to [(b) (4)] does not affect the bioavailability of your proposed product in humans has not been demonstrated. The simulation approach you have taken does not use any clinical data and is therefore not acceptable. Conduct an appropriate pharmacokinetic study in humans to investigate the effect of [(b) (4)] on the bioavailability of your product; you may use [(b) (4)] levels of [(b) (4)] %w/w or some other levels you deem appropriate to support your proposed specification limit for [(b) (4)].

   b. In order to conduct the study described in above, deviant formulations of Olaparib capsules with various percentages of [(b) (4)] will have to be manufactured. We recommend that the percentage of [(b) (4)] in the deviant formulations be quantified just prior to administration to patients and at the end of the study. You may also measure [(b) (4)] levels of the target and clinical deviant batches over a period of time to supplement the stability data that you are gathering.

c. **Submit, no later than 19-May-2014, the date when study data/results will be submitted**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
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/s/

RAJESH VENUGOPAL
05/12/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - Clinical Information Request
Date: Thursday, May 08, 2014 1:49:30 PM

Hi Darci,

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

We have identified a patient treated with olaparib on Study 24 (ID: E0001019) who was subsequently diagnosed with MDS/ trilineage dysplasia (2/14/11). We are unable to find a narrative for this patient. Please include this patient's narrative when you provide us with the previously requested update on cases of MDS (due 5/15/14).

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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RAJESH VENUGOPAL
05/08/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: Information Request: Patient AE information and CRF "backdating"
Date: Tuesday, May 06, 2014 2:21:38 PM

Hi Darci,

Our team has the following information Request that requires a response:

Re: Patient AE information and CRF "backdating"

1. We have identified 20 patients who have a > 6 month gap between the reporting of the start date of their last documented AE and the date of treatment discontinuation. Please confirm that there is no additional AE data for these patients:

D0810C00019/E0103009
D0810C00019/E0105006
D0810C00019/E0105009
D0810C00019/E0801001
D0810C00019/E0803008
D0810C00019/E0805002
D0810C00019/E1007001
D0810C00019/E1007004
D0810C00019/E1201001
D0810C00019/E1403005
D0810C00019/E1406001
D0810C00019/E1501001
D0810C00019/E1701005
D0810C00019/E1703012
D0810C00019/E1705001
D0810C00019/E1706007
D0810C00019/E1802001
D0810C00019/E1802003
D0810C00019/E1807004
D0810C00019/E1809001

2. Upon examination of the CRFs we noticed that some of the AE data were filled in and signed off by the investigator several months after the time the AE started. For example, the patient E0801001 had AE #003 started on 09/23/2009 and end on 11/3/2009. There appears to be someone's initial '(b) (6)' dated 11/4/09 and then the CRF was signed by the investigator, (b) (6)" on 4/4/2010. A random audit of several CRFs demonstrated similar findings of having the dated investigator's signature being several months after the AE end date. Please provide a detailed description of how the investigators were instructed to maintain the CRFs and clarify whether the investigators were entering AE data on the CRF forms in real time or whether there were periodic data entry points when the CRFs were filled out/signed.

Please respond **by 10 AM Monday, May 12**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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Office of Hematology and Oncology Products
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Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
05/06/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 - Olaparib Pharmacometrics Information Request
Date: Thursday, May 01, 2014 4:06:18 PM

Hi Darci,

Our Pharmacometrics review team has the following information request that require your response:

For exposure-response related datasets (ie, pk1pool.xpt, pk1eff.xpt, and pk1safe.xpt) submitted on April 15th, 2014, we request some new variables to be added into the corresponding datasets. Please respond within 3 business days to the following information request (by Tuesday, May 6 2014):

1. Include the efficacy variable PFS to pk1eff.xpt. You can assign -9999 for "not evaluated" and -8888 for "missing".
2. For pk1safe.xpt,
   - Add the following treatment related AE variables: ANAEMIA (including ANAEMIA MACROCYTIC and HAEMOLYTIC ANAEMIA), LEUKOPENIA, LEUKOCYTOSIS, LYMPHADENOPATHY, LYMPHOEDEMA, LYMPHOMA, LYMPHOPENIA, NEUTROPENIA, FEBRILE NEUTROPENIA, THROMBOCYTOPENIA, BLOOD AND LYMPHATIC SYSTEM DISORDERS, NAUSEA, CTC-GRADE3to5 NAUSEA, VOMITING, CTC-GRADE3to5 VOMITING. The following values can be assigned for the corresponding variables: 1 for Yes, 0 for No, -9999 for "not evaluated", -8888 for "missing".

   - Add WORST CTC GRADE for each of the following variables: ANAEMIA (including ANAEMIA MACROCYTIC and HAEMOLYTIC ANAEMIA), LEUKOPENIA, LEUKOCYTOSIS, LYMPHADENOPATHY, LYMPHOEDEMA, LYMPHOMA, LYMPHOPENIA, NEUTROPENIA, FEBRILE NEUTROPENIA, THROMBOCYTOPENIA, BLOOD and LYMPHATIC SYSTEM DISORDERS. Assign "NA" in case that WORST CTC GRADE is not applicable to a variable.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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/s/

RAJESH VENUGOPAL
05/01/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 - Olaparib - Clinical Pharmacology Information request
Date: Friday, April 18, 2014 2:24:47 PM

Hi Darci,

Our clinical pharmacology team have the following requests that require team's response:

1. For the ADME trial D0810C00010, please provide the location of the datasets that include individual and mean plasma and whole blood PK concentrations and parameters for total radioactivity in the edr. We note that the study report only includes information about the mean Cmax and Tmax of total radioactivity. Please submit a summary of other PK parameters for the total radioactivity as done for the olaparib moiety.
   Please respond by COB on April 25th, 2014.

2. For report "A Pooled Population PK Analysis for studies 1, 2, 8, 9, 12 and 24" dated 9 April 2014, submit the following datasets and your responses to the relevant EMA questions 103 & 104 **by COB on April 25th, 2014**:
   I. PredIndata.csv for run008sim.mod
   II. pk_pool_05march2014.csv for base.mod and final.mod. Note: pk1pool.xpt included in previous submission cannot be used to reproduce the results
   III. Run008Sim.txt for prediction.r
   IV. Your responses to the two EMA questions regarding the two population analysis reports (see appendix) since we have the same inquiries.

Appendix: EMA questions 103 & 104
Pharmacokinetics Question 103

Question: Analysis of pooled data from studies 02 and 07:

- The reporting of the analysis is not detailed enough to allow its evaluation. The applicant should provide details on the analyzed dataset (including the excluded data and the reasons for the exclusion) and the development of the covariate model.
- Besides the lack of information mentioned above, the relevance and usefulness of the analysis appears to be disputable for the following reasons:

o While, available data from NCA of rich data studies (studies 01 and 02) suggested strongly that the absorption of olaparib is saturable and limited by dissolution of olaparib a sequential zero order and first order model was used for the description of the absorption.
o A very high between-subject variability (>100%) is observed and remained unexplained by the model.
o The bioavailability was estimated to be 50 % lower in study 07 comparatively to study 02. The interpretation of such difference and the procedure used by the applicant to handle it are not clear. This aspect should be discussed further on the light of the inconsistency in development batches performances mentioned above. For instance, the applicant should indicate if different batches were used in both studies.

o The predictive capability of the model is not certain as no estimation of the shrinkage of the model is provided by the applicant.

Conclusively, the robustness of the developed model is not established and the prediction of systemic exposure made by the model and used in the PK-PD relationship investigation could not be considered reliable.

Pharmacokinetics Question 104

Question: Analysis of data from studies 02, 08, 09, 12 and 24:

The same model than that described and commented above (pooled data from studies 02 and 07) was used. Therefore, the same comments regarding the reliability of the model and the prediction made from it could be made.

Besides:

o The population parameters and their variability estimated by the refined model are not reported. Only parameters estimated for each study are reported.

o It is not clear why data from study 07 were not included in the analysis while these data where used in the development of the initial model. The applicant should justify the non inclusion of these data.

o Data from study 01 (conducted in Japanese patients) were not included in the analysis. The inclusion of such data is deemed to contribute to the elucidation of influence of ethnicity on olaparib PKs. The applicant should explain why the data from study 01 were not included in the analyzed dataset.

o The reported η shrinkage exceeds largely 25% for most of the parameters, attesting the poor predictivity of the model. Consequently, the prediction of the systemic exposure used in the investigation of PK-efficacy and PK-adverse event relationship could not be considered reliable.

o In addition, given that optimal plasma exposure to achieve clinical efficacy was proposed based on population PKPD for PARP-1 activity, the applicant should discuss the clinical implication of the high variability in PK parameters such as CL/F and the consequences on dosing recommendation: The added-value of concentrations monitoring and PD biomarker monitoring in clinical practice should also be discussed in this context.

o The influence of dose on baseline hazard as shown in table 32 is quite uncommon since the effect of dose = 200 mg is lower than that of dose = 100 mg and doses <100mg whereas there are increments for other doses: the applicant should discuss whether this is a reflection of a model misspecification or provide a scientific reason for this if there is any.

o Given that the influence of "study" factor on different PK and PD parameters is unexplained and could therefore be hardly replicate in real life, fitting and predictive performances of the PK and PD models should be shown without including this covariate.

Thank you.

rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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RAJESH VENUGOPAL
04/18/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 - Clinical Information Request
Date: Wednesday, April 16, 2014 2:38:19 PM

Hello Darci,

Our clinical review team has the following information request that require you immediate attention:

We are receiving preliminary reports from the FDA field inspector who is conducting a Bioresearch Monitoring Clinical Site inspection of the clinical sites in Boston, MA: Sites 1801 and 1802. The field inspector has noted numerous minor protocol deviations that were reported to the sponsor but have not been recorded in the protocol deviation section of the CSR (data listings). More concerning is that the field inspector has also discovered at least one Severe Adverse Event that also appeared to have been reported to the sponsor but is not found in the data listing and CSR tables. We request the following with a requested response as soon as possible. Your responses must address all study sites for study D018C00019.

1. Please provide any information you have regarding any discrepancy between any protocol deviations that have occurred at any site that is not reported in the CSR.
2. Please provide any information you have regarding any "filtering" of any reported protocol deviations (i.e. did you receive any reports of protocol deviations from the investigators but did not include them in the CSR for certain reasons?)
3. Please provide a summary of the different data cut-off dates that were used in generating the CSR. It is clear that the cut-off date for PFS was 30 June 2010 and for the updated OS, the cut-off date was 26 Nov 2012; however, for other data elements, were any other cut-off dates used?
4. Please provide any information you may have on any safety data that was reported to the sponsor but is not included in the CSR.
5. Please provide a detailed description regarding data management from clinical site source data, to CRFs, to information recorded in the application in study data file listings.

We request that you please respond as soon as possible.

Thank you for your attention to this matter.

Rajesh

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/s/

RAJESH VENUGOPAL
04/16/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib - Clinical Information Request
Date: Monday, April 14, 2014 3:51:31 PM

Hi Darci,

Our clinical team has the following MDS/AML information request that requires your response:

We are unable to verify the data you have submitted regarding the number of patients who have been diagnosed with MDS/AML following olaparib therapy. We note that only 11 out of the reported 16 patients who developed MDS/AML are found in the ISS dataset you have submitted. In the ISS dataset, 6 out of these 11 patients are identified as having developed MDS/AML by adverse event coding. According to Table 39 of the Summary of Clinical Safety, information regarding the development of MDS was taken from the AstraZeneca Patient Safety Database as opposed to the study datasets. Based on this information we request the following:

1. Please provide in detail, AstraZenca's approach in determining the number of patients who developed MDS/AML following olaparib therapy. Specifically address:
    a. Does AstraZeneca solely rely on investigators to report the development of MDS/AML in patients who have received olaparib when the event occurred after the end of safety follow-up, after the data cut off for the ongoing study, or after study closure?
    b. Has AstraZeneca received any other study reports to the AstraZeneca Patient Safety Database of MDS/AML that were not included in the Summary of Clinical Safety or ISS? Specifically, have there been cases that have been reported to AstraZeneca, but were reclassified with updated information? Have there been cases that were reported, but deemed to have been unrelated to olaparib treatment and thus not included in the provided summaries?
    c. You have provided an estimate of 2034 olaparib-treated patients. How did you derive this number?
    d. Has AstraZeneca received any reports of patients with prolonged cytopenias (of any type) to the Patient Safety Database? What analyses have you performed to determine whether there are any possible cases of MDS that may not have been diagnosed as MDS (i.e. reported cases of prolonged cytopenias that have not recovered, but where the investigator has not performed bone marrow evaluation)?

2. You have proposed to submit an updated number of patients who have developed MDS/AML in your 4MSU. Given the difficulties we have encountered in verifying the data, we request an updated analysis of the patients who developed MDS/AML by 5/15/14. In this analysis we request that you include the following:
    a. The responses to question 1
    b. An updated number of the patients who have developed MDS/AML with a data cut off on or near 5/1/14. Please include: Subject number, study number, cancer under treatment, dose of olaparib received, days on study treatment, diagnosis relative to end of olaparib treatment, BRCA mutation status, prior chemotherapy received, type of MDS/AML (chromosomal aberration), and outcome of MDS/AML.

c. Written narratives of any additional patients with MDS/AML that were not originally included in the SCS/ISS.

Please respond by **4 PM Thursday, May 15, 2014**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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RAJESH VENUGOPAL
04/14/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - CMC Information Request
Date: Monday, April 14, 2014 12:10:40 PM

Hello Darci,

Our CMC review team have the following comments that require a response from your team.

Lauroyl polyoxyl-32 glycerides (LMG) is the sole excipient in the drug product capsule formulation and acts as [redacted]. The submitted dog drug loading study summary (P.2.2, Table 2) indicates that a small change in the content of LMG (e.g. [redacted]% to [redacted]% drug loading) has a significant effect on the bioavailability of the active pharmaceutical ingredient [redacted]% to [redacted]%). Additional information regarding the excipient Lauroyl polyoxyl-32 glycerides (LMG) is needed.

1. Provide CMC information including specifications and CoA [redacted] for LMG lots used to manufacture the product used in the pivotal clinical trial and commercial product batches. Alternatively, provide LOA to the appropriate DMF.
2. Provide a table containing the manufacturing history of LMG lots for the clinical and commercial drug product lots – for example, Table 1 in Section P.5.4 Batch Analysis for Drug Product may be updated to include LMG lots.
3. Provide a description of observed variations in the LMG lots and the effect on quality attributes of the drug product – for example, bioavailability, [redacted], degradants, content uniformity or dissolution profile of the drug product. Discuss the robustness of the proposed manufacturing process and quality controls to manage variations in the excipient.
4. Provide data to demonstrate the effect of different LMG lots obtained from different suppliers on the proposed [redacted] to detect [redacted] in the drug product - spectra and analysis, including at the proposed lower limit of [redacted]%.
5. Since LMG can be [redacted] manufacturing process, include the attribute of [redacted] in the drug product release and stability specifications. While the in-process controls during the manufacturing process ([redacted] steps) produced 30+ lots with [redacted]%, the impact of [redacted] on the drug product stability (degradants, [redacted], etc) is not known at this time.

Please respond by 4 PM Monday, April 21, 2014.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
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RAJESH VENUGOPAL
04/14/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib - Clinical/Stats Information request
Date: Thursday, April 10, 2014 10:51:52 AM

HI Darci,

Our clinical and statistical team have the following information request that require your response:

Please provide the following for the pivotal trial 19.

1. Please provide following tables/figures for gBRCAm population (n=96).

Source	Table/Figure Title
CSR Table 8 (p81)	Summary of patient disposition at 26 November 2012 data cut-off
CSR Figure 2 (p82)	Flow chart of patient disposition
CSR Table 10 (p91)	Summary of important protocol deviations that may affect primary analysis
CSR Table 12 (p95)	Summary of demographic characteristics
CSR Table 13 (p96)	Summary of patient characteristics at baseline
CSR Table 14 (p98)	Summary of time from most recent disease progression to randomisation
CSR Table 15 (p98)	Summary of time from completion of final platinum chemotherapy to randomisation
CSR Table 16 (p99)	Summary of number of patients randomised within and after 8 weeks of completion of last platinum-containing therapy
CSR Table 17 (p101)	Summary of previous chemotherapy regimens at baseline
CSR Table 22 (p109)	Supportive and sensitivity analyses of PFS

2. Please provide a table to show summary of subsequent anti-cancer therapy in both FAS population and gBRCAm population.

3. Please provide SAS programs and datasets for sensitivity analyses of primary endpoint PFS to evaluate time bias and attrition bias in both FAS population and gBRCAm population.

4. Please perform the following sensitivity analysis of PFS in both FAS population and gBRCAm population.

    - Censoring rules are the same as those for the primary PFS analysis except that patients with subsequent anti-cancer therapy prior to progression were censored at the date of last disease assessment prior to subsequent anti-cancer therapy.

    Please also provide SAS programs and datasets for these analyses.

5. In both FAS population and gBRCAm population, please conduct an exploratory analysis to compare time from randomization to each tumor assessment (including unscheduled visit) using a log-rank test. When a patient missed a scheduled visit, his/her next visit time will be used to calculate the time to current assessment. Please report median of time to each assessment by treatment arm and log-rank test p-value (See Table 1). Please also provide SAS programs and datasets for this analysis.

Table 1. Median of Time to Tumor Assessment and Log-rank Test

Time from randomization to the	Median (n), in weeks		Log-rank Test
	Olaparib	Placebo	Nominal P-value
1st assessment			
2nd assessment			
3rd assessment			
…			

6. Please evaluate the effect of Olaparib among gBRCAwt patients (n=110). From the K-M curves of PFS for gBRCAwt in Figure 11.2.1.3.2.c (CSR Errata List Page 248), it appears that there is a violation of the proportional hazards assumption for treatment. If so, please use an appropriate method to analyze the PFS data for gBRCAwt patients. Please also provide SAS programs and datasets for your proposed analysis.

7. In both FAS population and gBRCAm population, please conduct an exploratory analysis to compare time from the start of the last platinum containing regimen that was given prior to olaparib therapy to date of progression using a log-rank test. In the case where the patient had therapy switched (i.e. changed therapy from carboplatin to cisplatin during the same regimen) please use the earliest date of that chemotherapy regimen. Please also provide the dataset containing the date you used for the time of start of last platinum regimen prior to olaparib/placebo therapy.

8. In FAS population, please conduct an exploratory analysis to compare PFS in the wt vs. gBRC A population in each respective arms (wtBRCA vs. gBRCA in placebo and wtBRCA vs. gBRCA in the olaparib arm). For the wtBRCA population, use only those patients who are confirmed to be wild type or VUS by local/Myriad testing (exclude patients who are unknown status).

Please respond **by 4 PM Friday, April 18**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

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/s/

RAJESH VENUGOPAL
04/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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 New Drug Application (NDA) dated February 3, 2014, received February 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for olaparib 50 mg capsules.

We also refer to your amendments dated February 6, 19, 27, March 13, 24, 25, 26, and 28, 2014.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is October 3, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 1, 2014. In addition, the planned date for our internal mid-cycle review meeting is May 6, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Pharmacometrics

In your March 12, 2014, response to the clinical pharmacology information request dated February 28, 2014, you stated that AstraZeneca is currently repeating both modeling exercises (i.e., population-PK/PD analysis and exposure-response analysis) based on comments from the European Medicines Agency. You also proposed to submit all the requested information prior to the end of April 2014. We requested to have all reports available by April 15, 2014, given the review timeline. We acknowledge your response during the application orientation meeting on March 28, 2014, that the updated population PK model would be submitted before April 15, 2014. Without further update on your exposure-response re-analysis timeline, a late submission of your updated exposure-response analysis could impact the review timeline.

Biopharmaceutics

The dissolution stability data have been reported at only the proposed specification time point of 45 minutes. Please submit, in Excel format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations, by April 21, 2014.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

1. White space should be present before each major heading in the highlights section. There must be no white space between the highlight heading and highlight limitation statement. There must be no white space between the product title and Initial U.S. approval date.

2. All contraindications listed in the Full Prescribing Information must also be listed in the highlights section or must include the statement "None" if no contraindications are known. The section heading "Contraindications" was not listed in the highlights section. If there are no contraindications, then you must state "None".

3. In the Table of Contents, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

4. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

   Currently, the Full Prescribing Information states in section 6.1, "(b) (4)", instead of "clinical trials…". Please correct.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 9, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (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:

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

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, call Rajesh Venugopal, Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMNA IBRAHIM
04/03/2014

From:	Venugopal, Rajesh
To:	"Bertelsen, Darci L"; Agosto, Teicher
Cc:	Jamieson, Roy
Subject:	RE: Olaparib NDA 206,162 - CMC Update Regarding RSM (b) (4), Response to IR Regarding Release Testing
Date:	Thursday, April 03, 2014 10:08:12 AM

Hi Darci,

Sorry your email was not responded to earlier. Your proposal is acceptable and we ask that you submit the revised RSM strategy (amendment to the NDA) by 4PM April 15, 2014 at the latest.

Thank you,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Wednesday, April 02, 2014 2:51 PM
To: Venugopal, Rajesh; Agosto, Teicher
Cc: Jamieson, Roy
Subject: RE: Olaparib NDA 206,162 - CMC Update Regarding RSM (b) (4), Response to IR Regarding Release Testing

Rejesh and Teicher,

Based upon Dr. Hakim's comment regarding the submission of a revised registered starting material (RSM) at the March 28, 2014 Olaparib NDA 206162 orientation meeting, we would just like to confirm that Dr. Hakim has seen the communication below and also confirm that our proposed submission is acceptable.

Thanks

Darci

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From: Bertelsen, Darci L
Sent: Thursday, February 27, 2014 10:32 AM
To: 'Venugopal, Rajesh'; 'teicher.agosto@FDA.HHS.gov'
Subject: Olaparib NDA 206,162 - CMC Update Regarding RSM (b) (4), Response to IR Regarding Release Testing

Rajesh and Teicher,

Reference is made to the email sent on January 9, 2014 from Rajesh and the subsequent AstraZeneca response (sent via email on January 14, 2014) regarding the registered starting material strategy for olaparib. Additionally, reference is also made to the communication from Teicher on February 26, 2014 regarding release testing at (b) (4). Please see AstraZeneca's

responses below:

CMC provision of revised Registered Starting Material (RSM) and [redacted] related modules

It is AstraZeneca's intention to provide revised modules covering our RSM strategy and [redacted] based on the following rational:

- RSM strategy – AstraZeneca believe selection of [redacted] as a suitable starting material is consistent with ICH Q11. However, we acknowledge the Agencies concerns and on further reflection believe it will be a difficult position to defend globally.

  AstraZeneca will submit, soon after NDA 206,162 is filed, a revised RSM strategy (impacting S.2, S.3.2, QOS modules) based on [redacted] as starting materials leading to formation of [redacted]. Additional details on this synthetic stage were provided in the AstraZeneca response to the Divisions December 3, 2014 information request (AstraZeneca response submitted to IND 75918, dated December 13, 2013, Serial No. 0646, Sequence No. 0589).

- [redacted]/validation (DS ID/[redacted] DP [redacted]) – AstraZeneca will submit, soon after NDA 206,162 is filed, enhanced modules incorporating more detail around the calibration model (impacting S.4.2, S.4.3, P.5.2, P.5.3 modules).

Would provision of revised modules soon after the NDA filing, covering a change in RSM strategy and additional [redacted] detail, be acceptable to the Agency?

Release Testing

In response to the following question from FDA: [redacted] is conducting the release testing for olaparib oral capsules. As outlined in NDA 206,162 Module 3.2.P.3.1 Manufacturer(s), Patheon Pharmaceuticals, Cincinnati will be performing Manufacturing [redacted] for Olaparib Capsules, 50 mg.

Can FDA please provide some additional information regarding why this question is being asked? It would be helpful to us to understand if there is any additional information we can provide or prepare for (e.g. Pre-approval Inspection) to help ensure timely responses.

Darci Bertelsen
US Regulatory Affairs Director

AstraZeneca
GRA | US Regulatory Affairs
C2C-717, 1800 Concord Pike, Wilmington DE, 19802

T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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/s/

RAJESH VENUGOPAL
04/03/2014

From: Fahnbulleh, Frances
To: "darci.bertelsen@astrazeneca.com"
Cc: "lori.chlysta@astrazeneca.com."
Subject: NDA 206162 (b) (4) - Proprietary Name Information Request
Date: Thursday, March 27, 2014 5:52:32 PM

Dear Mr. Bertelsen,

Reference is made to your NDA application submitted on February 3, 2014. Reference is also made to your request for review of the proposed proprietary name "(b) (4)". The review team has requested the following information:

Information Request for (b) (4) (Olaparib) 50 mg capsules

We are in the process of evaluating your proposed proprietary name, (b) (4) for Olaparib 50 mg capsules. We understand you are conducting a potential confirmatory clinical trial for a tablet formulation of Olaparib, which has a different strength, recommended dosage, and bioavailability then your Olaparib 50 mg capsule currently under NDA review. Your response to the information requests below will help us in our evaluation of (b) (4).

1. Provide the following information regarding your tablet formulation:

a. Dosage form

b. Strength

c. Proposed Indication(s)

d. Route(s) of Administration

e. Usual Dosage, Frequency of Administration, Dosing Interval, Maximum Daily Dose

f. Dose Modifications

g. Storage

h. How Supplied and Packaging Configuration

2. Describe your marketing plan for both proposed capsules and the tablet formulation. Include a timeline describing your plans for marketing just the 50 mg capsule, both capsule and tablet, or if there will be a transition to market only the tablet formulation.

3. If Olaparib capsule and tablet formulations are not therapeutically equivalent (e.g. cannot be substituted for each other) in clinical practice, then describe your plans for mitigating potential confusion and medication errors between the capsule and tablet

formulations.

Kindly acknowledge receipt of this email and provide a response by April 3, 2014.

Respectfully,

Frances Fahnbulleh

Frances Fahnbulleh, RPh, PharmD

Safety Regulatory Project Manager

Office of Surveillance and Epidemiology

CDER/FDA/WO22 , Rm#3471

Ph: 301-796-0942/ Fax 301-796-9906

email: Frances.Fahnbulleh@fda.hhs.gov

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/s/

FRANCES G FAHNBULLEH
03/28/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: Clin pharm/Pharmacometrics Information Request_03.14.14
Date: Friday, March 14, 2014 4:25:29 PM

Hello Darci,

Our clin pharm/Pharmacometrics review team have the following Urgent request:

- Submit the datasets **by March 28th** in response to the following IR that was sent on 02/28: "Include all PK concentration and parameter datasets for all the trials submitted in support of the clinical pharmacology package including Trials D0810C00001, D0810C00007, D0810C00009, D0810C00010 and D0810C00012". **Your proposed date of April 3rd does not give us sufficient time to decide on the whether your application can be filed**.
- Please clarify whether changes to the datasets, including the omitted concentration data in trial D0810C00010, would impact the data submitted in the study reports and whether you will need to submit updated study reports. If so, submit the updated study report(s) **by March 28th**.
- Submit all updated population PK/PD and exposure-response analysis reports, including scripts and datasets, **by April 15th** in response to the following IR that was sent on 02/28/2014 and your response to additional request sent on 3/12/2014. A late submission could impact the review timeline.

IR sent on 02/28/2014:

- *For the pharmacometric report dated 01 July 2013 by* (b) (6) *and titled "A pooled population analysis of the pharmacokinetic, efficacy and adverse event data obtained following dosing of olaparib capsule formulation to patients in D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024", please provide the following files:*

  1. *All scripts (including NONMEM control streams; SAS, R and/or S-plus codes) that were used to generate the results of the report.*

  2. *All datasets associated with above scripts. The datasets should include covariates that cover all available extrinsic and intrinsic factors such as concomitant medications, demographics, laboratories, etc.*

*Script files should be submitted as ASCII text files, and datasets should be submitted as SAS transport files with *.xpt extension (e.g.: er-ssc.txt, pooled_poppk_20130404.xpt*

Additional IR sent on 3/12/2014:

- *In your submission due by COB today for the response to the clinical pharmacology comments sent on February 28th, please include information regarding the exact problems with the datasets, analyses and reports, the comments received from the*

EU, exactly which datasets, models and reports will be updated and how different these updates are expected to be from those submitted. Please provide this information for both your proposed submissions as discussed in the Tcon today. Also please provide the new timelines associated with your updated submissions.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
03/14/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: Pharmacovigilance Information Request_03.14.14
Date: Friday, March 14, 2014 1:35:26 PM
Attachments: FDA Guidance E2E PV Planning 2005.pdf
FDA Guidance Good PV Practices and PE Assessment 2005.pdf

Hi Darci,

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

> *FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **olaparib** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the **NDA** application in the appropriate module so it can be reviewed accordingly.*

Please respond by **March 28, 2014, if not sooner**.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

44 pages of the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005) have been withheld. They can be found online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf and http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf

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RAJESH VENUGOPAL
03/14/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 Olaparib - Clinical Pharmacology Request
Date: Wednesday, March 12, 2014 2:27:38 PM

Hello Darci,

We hope that today's t-con was helpful to your team. Our clinical pharmacology team as the following request:

- In your submission due by COB today for the response to the clinical pharmacology comments sent on February 28th , please include information regarding the exact problems with the datasets, analyses and reports, the comments received from the EU, exactly which datasets, models and reports will be updated and how different these updates are expected to be from those submitted. Please provide this information for both your proposed submissions as discussed in the Tcon today. Also please provide the new timelines associated with your updated submissions.

- In addition please see comments regarding the PBPK reports and address whether the proposed timeline could be met.

  We conducted initial review of the PBPK study reports "Olaparib SimCYP1" and "Olaparib SimCYP2". Please submit the updated PBPK reports by addressing the following comments by **March 25, 2014**.

  1. You should provide justifications, assumptions and references for each input parameter in the Input Parameter Tables.

  2. You should include simulation results for pharmacokinetic studies being used to build/optimize the PBPK model. Specifically, your model should include (a) potential mechanisms responsible for the apparent nonlinear pharmacokinetics between 100 mg and 400 mg olaparib doses, (b) assignment of different elimination pathways given that unchanged olaparib was found in both urine and fecal samples in human mass balance study.

  3. The model should first be independently verified by comparing simulated effect of enzyme inhibitor or inducer on olaparib pharmacokinetics to the interim results of the ongoing drug-interaction studies with itraconazole and rifampin (if applicable). Any modification of the model after verification step should be documented and justified.

Additional simulations may be requested after we review the updated drug-interaction results and your updated PBPK reports

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
03/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

REQUEST FOR METHODS VALIDATION MATERIALS

AstraZeneca
Attention: Lori Chlysta
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Lori Chlysta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Olaparib Capsule, 50 mg.

We will be performing methods validation studies on Olaparib Capsule, 50 mg, as described in NDA 206162.

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

Method, current version

Drug Substance – Identification and (b) (4)
Drug Substance – Quantification of (b) (4)
Drug Substance – Assay by LC
Drug Substance – Organic Impurity by LC
Drug Substance – Particle size distribution by laser diffraction
Drug Product – Identification by LC
Drug Product – Assay by LC
Drug Product – Degradation products by LC
Drug Product – (b) (4)
Drug Product - Dissolution

Samples and Reference Standards

(b) (4)

Samples and Reference Standards Continued

(b) (4)

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

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

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
03/12/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: IR_Clinical Pharmacology NDA 206162 (Olaparib)
Date: Friday, February 28, 2014 8:21:07 AM

Hello Darci,

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

- Include all PK concentration and parameter datasets for all the trials submitted in support of the clinical pharmacology package including Trials D0810C00001, D0810C00007, D0810C00009, D0810C00010 and D0810C00012.
- For the pharmacometric report dated 01 July 2013 by (b) (6) and titled "A pooled population analysis of the pharmacokinetic, efficacy and adverse event data obtained following dosing of olaparib capsule formulation to patients in D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024", please provide the following files:

    1. All scripts (including NONMEM control streams; SAS, R and/or S-plus codes) that were used to generate the results of the report.
    2. All datasets associated with above scripts. The datasets should include covariates that cover all available extrinsic and intrinsic factors such as concomitant medications, demographics, laboratories, etc.

    Script files should be submitted as ASCII text files, and datasets should be submitted as SAS transport files with *.xpt extension (e.g.: er-ssc.txt, pooled_poppk_20130404.xpt

Please respond by **4 PM Monday, March 17, 2014**, if not sooner.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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RAJESH VENUGOPAL
02/28/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 (Olaparib) - Information Request
Date: Wednesday, February 19, 2014 11:28:08 AM

Hi Darci,

On behalf of our reviewers, please confirm the expected submission date of the final module for Myriad's PMA for the companion diagnostic to olaparib, as we would expect CDER and CDRH to make contemporaneous regulatory decisions for both the NDA and PMA applications.

Thank you,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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RAJESH VENUGOPAL
02/19/2014

From: Venugopal, Rajesh
To: darci.bertelsen@astrazeneca.com
Subject: NDA 206162 - Olaparib - Information Request
Date: Wednesday, February 12, 2014 11:58:57 AM

Hi Darci,

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

The patient safety narratives provided in Section 11.4 of the CSR are not sufficient, as they are simply line listings of information that would typically be included in the case report forms (including past medical history, surgical history, concomitant meds, baseline characteristics, dates of AEs, etc). You should resubmit your patient narratives, providing the clinical scenario leading up to the event in question (i.e. death, SAE, discontinuation). These should be in a format that contains sentences within paragraphs to describe the event in question.

Please respond by 4 PM Tuesday, February 18, 2014. Please note, FDA will be closed on Monday February 17.

Thanks,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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Fax: (301) 796-9845

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RAJESH VENUGOPAL
02/12/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Subject: RE: NDA 206162 Acknowledgement letter
Date: Monday, February 10, 2014 11:12:21 AM

Hi Darci,

In order for our IRT/QT reviewers to review your clin/pharm data please be mindful of the following:

1. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and ΔΔQTc (time-matched drug-placebo difference in QTc interval, baseline adjusted). Based upon this relationship, the predicted population average ΔΔQTc and its corresponding upper 95% 1-sided confidence interval bound may be computed at appropriate concentrations, e.g., the mean maximum plasma concentrations under therapeutic and supratherapeutic doses or other concentrations of interest. In addition to the above analysis, there may be merit in considering alternative dependent variables such as QTc or ΔQTc (baseline-adjusted) to derive the ΔΔQTc endpoint.

We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

2. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
   a. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
   b. Baseline and on-treatment ECGs should be based on the same lead

3. When you submit your 'QT study' report, please include the following items:
   a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b. Electronic copy of the study report
   c. Electronic or hard copy of the clinical protocol
   d. Electronic or hard copy of the Investigator's Brochure
   e. Annotated CRF
   f. A data definition file which describes the contents of the electronic data sets
   g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure response analyses
   h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a

specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID
(link to waveform files if applicable)
i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any:
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study
    k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
    l. A completed Highlights of Clinical Pharmacology Table

4. Advancing in this field – and possibly reducing the burden of conducting QT studies– depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data,
available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library .

Any questions let me know.

Thanks,
Rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, February 07, 2014 9:37 AM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 Acknowledgement letter

Yes we are working on that now to ensure we can provide the most data to you within 120 days of submission. Just to confirm that would be the end of May/early June.

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, February 07, 2014 9:35 AM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 Acknowledgement letter

Also Darci,

Our clin/pharm folks want to confirm as per your NDA cover letter that you will provide/submit the clinical pharmacology data as an amendment within 120 days of February 3 submission of the original NDA?

Thanks,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Friday, February 07, 2014 9:31 AM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 Acknowledgement letter

Not a problem. I understand.

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, February 07, 2014 8:57 AM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 Acknowledgement letter

Thanks Darci. I saw the submission. I would have been fine with it but things need to be official around here, obviously.

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Wednesday, February 05, 2014 1:33 PM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 Acknowledgement letter

I will do that right away.

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 1:26 PM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 Acknowledgement letter

Hi Darci,

Technically, we are supposed to send letters and correspondences to the individual stated on the 356h form. That would be Barry Sickels. If you are the one correspondences should be sent to then could you please send an official correspondence to this NDA stating that all correspondence

should come to you? That way, it can be official and we know to send things to you. If you had that stated in the cover letter then it would have been enough. But since it wasn't we will require correspondence stating so.

Thank you,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Wednesday, February 05, 2014 10:23 AM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 Acknowledgement letter

Thanks Rajesh

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 10:19 AM
To: Bertelsen, Darci L
Subject: NDA 206162 Acknowledgement letter

Hi Darci,

Attached please find our acknowledgement letter stating receipt of your NDA submission.

Regards,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 2171
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
02/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

NDA ACKNOWLEDGMENT

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

Dear Ms. Bertelsen:

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: Olaparib

Date of Application: February 3, 2014

Date of Receipt: February 3, 2014

Our Reference Number: NDA 206162

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 4, 2014, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

Sincerely,

{See appended electronic signature page}

Rajesh Venugopal, MPH, MBA
Regulatory Project Manager
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/

RAJESH VENUGOPAL
02/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075918

MEETING MINUTES

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 the meeting between representatives of your firm and the FDA on October 2, 2013. The purpose of the meeting was to discuss the content and format of an NDA to support the treatment of patients with gBRCA mutated ovarian cancer.

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

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

Sincerely,

{See appended electronic signature page}

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

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 2, 2013/1:00 PM-2:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 075918
Product Name:	Olaparib (AZD2281, KU-0059436)
Indication:	Maintenance treatment of adult patients with platinum sensitive relapsed germline BRCA (gBRCA) mutated ovarian cancer (including fallopian tube or primary peritoneal) in response (complete response or partial response) to platinum-based chemotherapy.
Sponsor/Applicant Name:	AstraZeneca Pharmaceuticals LP
Meeting Chair:	Amy McKee, MD
Meeting Recorder:	Rajesh Venugopal, MPH, MBA

FDA ATTENDEES
Anthony Murgo, MD, Acting Director, DOP1
Amy McKee, MD, Medical Team Leader, DOP1
Geoffrey Kim, MD, Medical Officer, DOP1
Julia Beaver, MD, Medical Officer, DOP1
Elimika Pfuma, PharmD, PhD, Clinical Pharmacology, DOP1
Qi Liu, PhD, Clinical Pharmacology Team Leader, DOP1
Todd Palmby, PhD, Acting Pharm/Tox Supervisor, DHOT
Ali Al Hakim, PhD, CMC Branch Chief, ONDQA
Gaetan Ladouceur, PhD, CMC Reviewer, ONDQA
Shenghui Tang, PhD, Statistics Team Leader, DBV
Stella Karuri, PhD, Statistics reviewer, DBV
Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1
Eunice Lee, PhD, PACB/DIHD/OIR/CDRH

Reena Philip, PhD, Deputy Division Director, DIHD/OIR/CDRH
Elizabeth Mansfield, PhD, Director of Personalized Medicine, OIR/CDRH
Hui Lee Wong, PhD, PACB/DIHD/OIR/CDRH
Frances Fahnbulleh, RPh, PharmD, Regulatory Project Manager, OSE
Robert Becker, PhD, OIR, CDRH

EASTERN RESEARCH GROUP ATTENDEES

(b) (6), Independent Assessor
(b) (6), Independent Assessor
(b) (6)

SPONSOR ATTENDEES

Jane Robertson, MB BS, MD, Executive Global Clinical Director
Anitra Fielding, MB ChB, Medical Science Director, Oncology
Helen Swaisland, BSc, Principal Clinical Pharmacology Scientist
Debbie Mackenzie, BSc, MSc, Global Regulatory Leader
Darci Bertelsen, BA, US Regulatory Affairs Director
Cindy Lancaster, MS, MBA, JD, Executive Director, Global Regulatory Affairs
Hesham Abdullah, MD, MSc, RAC, VP, Global Regulatory Affairs, Oncology
Maria Orr, BA, MA, PhD, Diagnostic Team Director
Antoine Yver MD MSc, VP, Global Medicines Development Head, Oncology and New Opportunities
Tony Ho, MD, Global Product Vice President Olaparib, Oncology

BACKGROUND

The purpose of this meeting is to discuss AstraZeneca's intention of submitting a New Drug Application for olaparib for the maintenance treatment of patients with platinum-sensitive, relapsed, germline BRCA-mutated ovarian cancer in response to platinum-based chemotherapy. AstraZeneca is partnering with Myriad Genetic Laboratories Inc. to develop a companion diagnostic assay to olaparib: the Integrated *BRACAnalysis* test.

Olaparib (AZD2281, KU-0059436) is a potent oral inhibitor of polyadenosine 5'-diphosphoribose polymerases (PARP-1 and -2). These PARP enzymes are required for the efficient repair of DNA single strand breaks. During the repair process, PARP auto-modifies itself and dissociates from the DNA to facilitate access for other repair enzymes. Olaparib inhibits the action of PARP by preventing this dissociation, trapping PARP on the DNA and blocking repair of the single strand break, resulting in increased genomic instability and cancer cell death.

Study D0180C00019 (Study 19), is a multicenter, randomized, double-blind, placebo-controlled study of olaparib monotherapy as maintenance treatment for patients with platinum sensitive relapsed (PSR) serous ovarian cancer. The study randomized 265 patients with a primary endpoint of progression free survival (PFS). Study 19 demonstrates in the intent-to-treat primary analysis a 65% reduction of risk of death or disease progression (HR 0.35; 95% CI 0.25-0.49; $p<0.00001$), with median PFS of 8.4 and 4.8 months in the olaparib 400 mg PO BID and placebo

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arms, respectively. A planned subgroup analysis by BRCA mutation status, as determined by germline or somatic mutation status, demonstrates a 82% risk reduction in disease progression or death and a median PFS for olaparib-treated patients 6.9 months longer than for placebo treated patients (PFS HR 0.18; 95% CI 0.11-0.31; p<0.00001, median 11.2 versus 4.3 months).

On May 15, 2013, FDA informed AstraZeneca that the results of Study 19 may provide the basis for an NDA for accelerated approval of olaparib as maintenance therapy for patients with platinum sensitive, gBRCA-mutated ovarian cancer that has responded to platinum-based chemotherapy in the platinum-sensitive setting. Other key meetings that have been held include a Type C meeting on October 23, 2012, to discuss the olaparib development plan in patients with gBRCA mutated ovarian cancer and a pre-submission meeting held on March 18, 2013, to discuss the development of the Myriad BRCAnalysis companion diagnostic.

DISCUSSION

1. *Based on the chemistry and biopharmaceutics package presented, does the Agency agree with the proposed strategy* [redacted (b) (4)]

   FDA Response: **No. The significant increase of the** [redacted (b) (4)] **of olaparib observed in the stability studies should be further investigated and controlled to ensure that it will not occur during the proposed shelf-life of the drug product. Therefore, we recommend the following:**

   a. **Provide a rationale for the** [redacted (b) (4)] **observed in the olaparib drug product.**

   b. **Add a test with an acceptance criterion for** [redacted (b) (4)] **in the drug product specification. Provide a justification with supportive data for your proposed limit of** [redacted (b) (4)] **in the olaparib drug product.**

   c. **The test for** [redacted (b) (4)] **in the drug substance specification should be performed only after the** [redacted (b) (4)] **process.**

   d. **Provide a justification for the acceptance criterion of** [redacted (b) (4)] **in the drug substance specification based on test data from multiple batches.**

   e. **Provide the drug substance batches used to manufacture the 14 in-life batches of drug product analyzed for** [redacted (b) (4)]**. Also, provide the level of** [redacted (b) (4)] **analyzed by** [redacted (b) (4)] **for each of these drug substance batches.**

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Meeting Discussion: The Agency strongly recommended that the Sponsor request a separate CMC-only meeting to discuss the NDA submission. The Sponsor proposed to submit a CMC data package to the Agency through the IND prior to the NDA submission. The Agency indicated that this is acceptable and requested that it be submitted by the end of October.

2. *AstraZeneca proposes to submit the stability data from the proposed stability shelf-life confirmation testing programme to the NDA Annual Report. Is this acceptable to the Agency?*

FDA Response: The proposed shelf-life and storage conditions of olaparib drug product will be a review issue based on the information available at the time of the NDA application.

Meeting Discussion: No discussion took place.

3. *Does the Agency agree that the completed package of preclinical toxicology studies provides sufficient data to support initial registration for the use of olaparib as maintenance therapy in platinum sensitive relapsed (PSR) patients with gBRCA mutated ovarian cancer?*

FDA Response: We agree that the completed nonclinical toxicology studies appear sufficient to support an NDA submission for the proposed indication of maintenance treatment of patients with platinum-sensitive relapsed gBRCA mutated ovarian cancer in response to platinum-based chemotherapy. However, the adequacy of the nonclinical data to support approval for the proposed indication will be determined following our review of the data included in the NDA submission.

Meeting Discussion: No discussion took place.

4. *Does the Agency agree that the clinical evidence base described in the briefing document is appropriate to support the risk benefit assessment of olaparib capsules as a maintenance treatment for patients with gBRCA mutated, platinum-sensitive relapsed ovarian cancer*?

FDA Response: This is a review issue. The Agency informed the sponsor that consideration of accelerated approval could be given to olaparib capsules as maintenance treatment for patients with gBRCA mutated, platinum-sensitive, relapsed ovarian cancer due to observed median PFS improvement of 7.1 months and hazard ratio of 0.17 in the gBRCA-mutated population treated with olaparib in Study 19. There are several concerns regarding the suitability of this trial to provide sufficient evidence for a meaningful therapeutic benefit over existing treatments and are as follows:

1) The clinical benefit of a PFS improvement in the maintenance setting.

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2) **The limited number of patients in the gBRCA mutation subset (53 patients on the olaparib treatment arm and 43 patients on the placebo arm).**

3) **The retrospective, post-hoc nature of determining the gBRCA population.**

4) **The methods used to determine gBRCA status in Study 19 (Myriad, local, (b) (4) tissue-based assay).**

5) **Potential bias due to disproportionate distribution of the type of BRCA mutation (i.e. BRCA1 vs. BRCA2) between the olaparib treatment arm and placebo arm.**

6) **The change in olaparib formulation and any associated changes in the safety and tolerability profile from the capsule formulation, used in Study 19, to the tablet formulation, proposed for the potential confirmatory trial, Study 2.**

In order to strengthen the application, you should make every effort to define clearly for each patient: BRCA mutation status, tissue vs. germline BRCA mutation, type of BRCA mutation (BRCA 1 vs. BRCA2; nature of mutation, e.g., frameshift mutation at codon x), type of BRCA mutation test used to define status (Myriad, local, (b) (4)) and whether the mutation has been confirmed by the Myriad test. For those patients enrolled in Study 19, you should define whether BRCA mutation status was known prospectively or whether it was defined retrospectively. In addition, every attempt should be made to provide the above information regarding each patient's BRCA mutation status in datasets for Studies 41 and 12. Data regarding dose adherence and ability to tolerate daily administration of olaparib also would be helpful.

Meeting Discussion: No discussion took place.

5. *Does the Agency agree that the stated data cut-off and pooling approach for clinical safety data are appropriate for review and will provide for an adequate assessment of the safety of olaparib for the proposed indication?*

FDA Response: Your approach appears acceptable.

Meeting Discussion: No discussion took place.

6. *Does the Agency agree with the proposal for meeting the requirements of the ISE and ISS in the NDA?*

FDA Response: Yes.

Meeting Discussion: No discussion took place.

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7. *Does the Agency agree with the proposal for providing the available clinical pharmacology data at the time of the initial NDA submission, to supplement the NDA with additional data during the review period, and that additional data be provided as a post marketing commitment?*

   FDA Response: No. In addition to trials listed in Table 13, in the initial NDA submission include the clinical study reports for the food effect trial (D081A00001), the DDI trials (D081600007 and D081600008) and the QT evaluation portion of Trial # D081600004. Submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock.

   Meeting Discussion: The Agency requested that the Sponsor submit the interim study reports for trials 001, 007, and 008 and QT data within 120 days of the NDA submission. Also, the Agency requested that the Sponsor submit the models used for the prediction of DDIs in the original NDA application.

8. *AstraZeneca would like to confirm that the global Phase III study (D0816C00002) of olaparib tablets in patients with BRCA mutated platinum-sensitive relapsed ovarian cancer, which will be ongoing at the time of the NDA submission, is appropriate as the confirmatory study to support full approval?*

   FDA Response: If this confirmatory trial does not meet its primary endpoint, please discuss your plans for continued marketing of this drug and further development.

   As the confirmatory Phase 3 trial is planned using a tablet formulation that is not bioequivalent to the current capsule formulation, please clarify if your plan would be to continue to market the capsule formulation.

   The overall design of Study 2 appears to be appropriate as a confirmatory study; however, we reiterate our advice given in the October 23, 2012, response to Question 2 that a statistically significant difference in PFS improvement may not demonstrate a clinically meaningful difference. In addition, we do not recommend the inclusion of patients with a tumor-associated BRCA deleterious mutation without germline BRCA mutation in this study. The activity of olaparib in patients with somatic, deleterious BRCA mutations in the absence of germline BRCA mutations is provocative; these patients, as well as the associated companion diagnostic, should be studied in a separate trial in a prospective manner.

   In Study 2, subjects will be randomized into the trial based on previously identified BRCA mutations (from local testing) or by prospective testing at Myriad. It is noted that samples from some patients (e.g., from China) will not be tested at Myriad. You should specify what proportion of subjects will have been previously tested, what proportion will be prospectively tested, and the expected frequency without samples tested at Myriad (i.e., how many from China, how many with tBRCA results only). The diagnostic analysis for gBRCA mutations should account for missing data. You also

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should clarify how discordant results (e.g., between local testing and Myriad testing methods) will be resolved.

Meeting Discussion: No discussion took place.

9. *Would the Agency consider it acceptable to review the NDA dossier in the absence of a PMA, or would this be a reason for a refusal to file?*

FDA Response: The ability to file the application is a review issue. The Agency is expecting the NDA application and the PMA application to be filed within a reasonable time period of each other.

Meeting Discussion: The Sponsor proposed for the companion diagnostic PMA to be submitted in second quarter, 2014. The Agency suggested that this may not provide enough time for substantive review and suggested that the Sponsor meet with CDRH to discuss a modular PMA submission as soon as possible. The Agency noted that submission of the PMA shell can occur prior to the NDA submission. The Sponsor plans to submit the NDA sometime in November or December 2013. The Agency reiterated that this application likely will be discussed at an Advisory Committee meeting.

10. *Would the Agency be able to provide NDA approval in the absence of a PMA?*

FDA Response: It is premature to answer this question at this time without further discussion with the manufacturer of the companion diagnostic as to the rate-limiting factors precluding a PMA submission. We recommend a separate meeting that includes Myriad to address this question.

We strongly recommend that approval of the companion diagnostic device is contemporaneous with the approval of the therapeutic product if the diagnostic is essential for the safe and effective use of the drug. An approved IDE may not be used to support the use of an investigational device for an approved therapeutic indication (per 21 CFR 812.7).

CDRH will be happy to work with the diagnostic sponsor on some of the rate-limiting steps in order to facilitate the PMA review process.

Meeting Discussion: No discussion took place.

11. *Does the Agency agree with the proposed content/format for individual study datasets and pooled summary datasets?*

FDA Response: Your plan appears acceptable.

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Meeting Discussion: No discussion took place.

12. *Does the Agency agree that the stated pooling approaches for safety data from the various trials are appropriate for review and will provide for an adequate assessment of the safety of olaparib?*

FDA Response: Your plan appears acceptable.

Meeting Discussion: No discussion took place.

13. *Does the Agency agree with the proposal that patient narratives will not be provided for deaths due to progression of the condition under study?*

FDA Response: No. Narratives for all patients who died within 28 days of the last dose of olaparib should be provided regardless of attribution of death, in addition to those patients you have proposed.

Meeting Discussion: No discussion took place.

14. *Does the Agency agree that the proposed Table of Contents is appropriate and sufficient to support review of the NDA?*

FDA Response: From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- **Do not create additional nodes in the eCTD structure beyond what is in the specifications (e.g. m1.2.1 – m1.2.6). FDA FORM 3674 and the rest of the documents can reside under m1.2 cover letter section as separate document from the cover letter but with clear leaf titles, indicating the content of the document.**

- **For archival purposes, you should submit a pdf file of any labeling document submitted in Word. Also, when you submit Word documents, make sure the leaf title includes "word", so reviewers could quickly identify the Word version of the document.**

- **Providing a single 3.2.S and 3.2.P Manufacturing section with attribute of "ALL" and differentiating documents by leaf title, is acceptable. Additionally, indicating the substance/product/manufacturer name at the beginning or end of a leaf title, helps sorting abilities when sorting by substance/product/manufacturer.**

- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.**

Reference ID: 3384713

- **Do not provide placeholders for sections that will not be submitted (e.g. 4.2.3.7. Other Toxicity Studies, N/A). Placeholders are only required when submitting ANDAs.**

- **Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf**

- **Regarding use of the m5-3-7 heading element, FDA doesn't use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml.**

Meeting Discussion: No discussion took place.

15. *AstraZeneca would like to offer an Orientation Session 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.

Meeting Discussion: No discussion took place.

ADDITIONAL MEETING DISCUSSION:

The Sponsor noted that they have initiated both the confirmatory trial in platinum sensitive maintenance ovarian cancer as well as the Phase 3 trial in frontline maintenance treatment of ovarian cancer.

PREA REQUIREMENTS

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

Reference ID: 3384713

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
10/04/2013

AMY E MCKEE
10/07/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 26, 2014

TO: NDA 206162

FROM: Rajesh Venugopal

SUBJECT: The NDA PDUFA V Late-Cycle Meeting Canceled

APPLICATION/DRUG: NDA 206162 Lynparza (olaparib)

The purpose of this memo is to indicate that a Late-Cycle Meeting between the Agency and Applicant for NDA 206162 Lynparza (olaparib) for December 2, 2014, was canceled as per the Applicant's request.

The Agency sent the Applicant our Late-Cycle Meeting background package on November 20, 2014. On November 26, 2014, the Applicant communicated to the Agency (see email attached) that they would like to cancel the Late-Cycle Meeting with the Agency.

We discussed the Applicant's decision to decline the Late- Cycle Meeting with the Office of New Drugs Immediate Office (OND IO) and the OND IO decided that the Late-Cycle Meeting with the Applicant could be canceled.

From: Bertelsen, Darci L
To: Venugopal, Rajesh
Cc: Chlysta, Lori A; Jamieson, Roy
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package
Date: Wednesday, November 26, 2014 7:40:23 AM

Good Morning Rajesh,

The team has reviewed the response below and agrees that it is clear and no Late Cycle Meeting will be required from an AstraZeneca position.

Therefore, we agree to cancel the NDA 206162 Late Cycle Meeting currently scheduled for December 2, 2014 from 3 to 4 p.m.

Written confirmation of AstraZeneca's agreement to cancel this meeting will be submitted next week via the electronic gateway to complete the NDA review file.

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Tuesday, November 25, 2014 9:30 AM
To: Bertelsen, Darci L
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Hello Darci,

The proposed approach to provide results (b) (4) for the degradant, (b) (4), is appropriate. The acceptability of the (b) (4)

If your group accepts our response and wish not to have a face to face OR a teleconference Late Cycle Meeting then please decline in writing so that we may have documentation of this for our records for this NDA. Please note that if a teleconference is required we unfortunately cannot move the time to the morning hours on December 2.

Regards,
rajesh

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, November 24, 2014 12:45 PM
To: Venugopal, Rajesh
Cc: Chlysta, Lori A
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Rajesh,

AstraZeneca agree to comply with the FDA conditions outlined in the 3 outstanding substantive CMC review issues listed in the Late Cycle Meeting Background Package, namely;

- Acceptance criteria for degradant (b) (4)
- (b) (4) testing
- Stability study as post-marketing commitment

Additional detail around the AstraZeneca position and proposals are presented below;

1. The proposed NMT (b) (4)% acceptance criteria for the content of the degradant, (b) (4), in olaparib capsules at end of expiry is not qualified. FDA advises that the acceptance criteria should be (b) (4)%.
Please note that the acceptance criteria has been set at (b) (4)% in line with the ICH Q3B qualification threshold for degradants in drug product. A revised specification Module 3.2.P.5.1. Specifications is attached.

2. The proposed exclusion of (b) (4) testing for (b) (4) at release of olaparib capsules is not acceptable. FDA advises that insufficient data have been provided to support the exclusion of (b) (4) testing and that all lots should be tested at release.
A revised specification Module 3.2.P.5.1. Specifications is attached reflecting that (b) (4) testing will be routinely performed at release.

3. As a post-marketing commitment, conduct a stability study with the process validation batches (3) with ICH primary stability testing to the submitted specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to (b) (4) months.
This commitment, included in the initial NDA, was the subject of a recent interaction (sequence 0056) where AstraZeneca re-confirmed its approach to conduct a repeat ICH stability study on the process validation batches and agreed mutually acceptable delivery dates for interim and final study reports. Please note the study will be performed up until (b) (4) months which is the agreed drug product shelf-life.
Regarding review issue 1, the Agency has stated that its position on this limit is driven by a lack of qualification of the degradant by toxicological studies or clinical experience. AstraZeneca is (b) (4) For this, and in accordance with ICH guidance (ICH Q3B (R2) Impurities in New Drug Products, 2006), AstraZeneca would (b) (4) . AstraZeneca considers that conducting further genotoxicity studies for the degradant to be unnecessary, as in SAR evaluation this degradant was shown to possess no

alerts of concern, and olaparib itself has been shown to be genotoxic through its mechanism of action (PARP inhibition).

Whilst AstraZeneca currently proposes to accept a (b) (4)% end of life specification as the Agency requests, AstraZeneca would like to confirm that (b) (4) .

Please could the Agency provide written confirmation that this approach is an acceptable (b) (4) degradant specification?

If written confirmation is received in advance of the December 2, 2014 Late Cycle Review Meeting, then AstraZeneca will decline the meeting.

If the Division is unable to provide written confirmation in advance of the scheduled meeting on December 2, 2014, then AstraZeneca requests that the meeting format be a teleconference. The proposed AstraZeneca participants are:

Hesham Abdullah – Regulatory Vice President, Oncology Therapy Area
Debbie Mackenzie – Global Regulatory Affairs Director
Roy Jamieson – CMC Regulatory Affairs Director
Jim Murray – Pharmaceutical Development, Project Director
Steve Horner – Nonclinical Principal Scientist
Kieran McKillop – Global Supply Chain
Tony Ho – Global Product Vice President
Darci Bertelsen – US Regulatory Affairs Director

Lastly, based upon the proposed AstraZeneca attendees and the limited scope of the meeting, would it be possible to move the teleconference to the morning hours as several of the team members are located in Europe.

Thanks in advance, and as always, please don't hesitate to contact me if you need any additional information.

Darci Bertelsen
Regulatory Affairs Director

AstraZeneca
GRAPSQA | Regulatory Affairs
1800 Concord Pike, Wilmington DE, 19802
T: (302) 886-7355 F: (302) 886-2822 M: (b) (6)
darci.bertelsen@astrazeneca.com

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:59 PM
To: Bertelsen, Darci L
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Dec. 2, 3-4 PM

From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Thursday, November 20, 2014 3:43 PM
To: Venugopal, Rajesh
Subject: RE: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Can I ask a quick question.

What time during the day is the meeting scheduled for?

Darci

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From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Thursday, November 20, 2014 3:30 PM
To: Bertelsen, Darci L
Subject: NDA 206162 (Olaparib) Late Cycle meeting Briefing Package

Hi Darci,

Attached please find our briefing package for the Late Cycle meeting scheduled currently for December 2. Once you've had a chance to review the document please let me know if you still require a face to face meeting or if a teleconference would be enough. If you feel you do not require either one and you are fine with what's stated in the document then please let me know as well. A copy of this document is also being mailed to you.

Thanks,
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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/s/

RAJESH VENUGOPAL
12/02/2014

From: Venugopal, Rajesh
To: "Bertelsen, Darci L"
Subject: RE: Olaparib - CMC Overview Submission
Date: Tuesday, December 03, 2013 11:37:56 AM

Hi Darci,

The CMC reviewers and the biopharmaceutics reviewer has reviewed your CMC overview document and here are their comments:

CMC Comments:

The following CMC issues should be addressed prior to the NDA filing:

1. There is not enough information in the meeting package to make a determination on the acceptability of (b) (4) as the starting material. Provide a detailed synthetic scheme for the custom synthesis of (b) (4) starting material and a discussion on (b) (4) impurities along with purging studies.

2. The comparison study on (b) (4) drug substance batches appears inconclusive for the determination of the (b) (4) changes because all 6 batches tested (Tables 9-11) have levels of (b) (4) below the detection limit. In order to substantiate your claims that no significant changes occur during the (b) (4) process, you must include batches with measurable amount of (b) (4) (above the limit of detection) in the tested (b) (4) batches, such as batch C589/8 and (b) (4) 1. Until data from those batches corroborate your claims, testing for (b) (4) should only be performed on (b) (4) batches of drug substance.

In addition, include the following changes in your NDA application:

3. Because heavy metals can be present in various sources of a manufacturing process, such as reagents and solvents, add a test and an acceptance criterion for heavy metals in the specification of olaparib drug substance.

4. We recommend using a simpler nomenclature (preferably abbreviated codes) when referring to intermediates, starting materials, related impurities and degradants.

5. In section S.3.2, discuss in more details the fate of (b) (4) as a potential impurity of the drug substance.

6. Provide data from a minimum of 10 batches when proposing to exclude solvents (b) (4)) from the drug substance specification.

7. Provide a mechanism for the formation of the (b) (4) degradant observed in the drug product stability studies.

Also, it is noted that the proposed drug product specification limit of (b) (4) % for (b) (4) degradant is above the qualification threshold of (b) (4) % according to the ICH Q3B guidance. The acceptability of the proposed specification limits will be a review issue.

Biopharmaceutics Comments:

1. Polysorbate 80 has been chosen as the surfactant in the dissolution medium to aid solubility of the drug substance and to assure sink conditions throughout testing. Due to huge variability observed at (b) (4), were additional experiments conducted with other surfactants? If so, please include results of assessment of other surfactants in the NDA.

2. Please give additional details on the drug loading experiments in the investigation of the discriminating ability of the dissolution method, such as the quantitative composition of the variants of the target formulation. As presented, it is not clear if drug loading is a process change or a critical attribute in the manufacturing of the drug product.

3. Refer to the general biopharmaceutics advice provided below, paying particular attention to experimental details on the dissolution method development and rationale for proposing acceptance criteria using the clinical batch and primary stability batches:

We have the following comments for the information that should be provided in your NDA regarding the development of dissolution method and establishing dissolution acceptance criteria for your product:

1. Dissolution Testing: Include the dissolution method report supporting the selection of the proposed test. This report should include the following information:

a. Solubility data for the drug substance as a function of pH range;

b. Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be specified clearly. If possible, the dissolution profile should be complete and cover at least (b) (4) % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time points) is reached. We recommend use of at least twelve samples per testing variable;

c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative drug release with time; and

d. Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

e. Include also the data supporting the robustness of the proposed dissolution test and the validation data for the analytical method used to assay the dissolution samples (precision, accuracy, linearity, stability, etc.).

The dissolution method report may also be provided under the IND for review and comments.

2. Dissolution Acceptance Criterion(a): For the setting of the dissolution acceptance criterion(a) of your proposed drug product, the following points should be considered:

a. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug product [*i.e., sampling time point and limit*].

b. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

c. The selection of the specification time point should be where Q = (b) (4)% dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2 or 4, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where Q = (b) (4)% dissolution occurs.

d. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criteria for your proposed product will be made during NDA review process based on the provided data.

Regards,

Rajesh

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From: Bertelsen, Darci L [mailto:darci.bertelsen@astrazeneca.com]
Sent: Monday, November 18, 2013 3:09 PM
To: Venugopal, Rajesh
Subject: Olaparib - CMC Overview Submission

Hello Rajesh,

I just wanted to check in with you to see how the review of the CMC overview document (submitted on October 31, 2013; Serial No. 634, Sequence No. 0577) by Dr. Hakim and Dr. Ladoucher is going and if there is any additional information they need from AstraZeneca.

Darci Bertelsen
US Regulatory Affairs Director

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/s/

RAJESH VENUGOPAL
12/03/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206162

LATE CYCLE MEETING
BACKGROUND PACKAGE

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lynparza (olaparib) 50 mg capsules.

We also refer to the Late-Cycle Meeting (LCM) scheduled for Tuesday, December 2, 2014. Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Acting Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, December 2, 2014
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: NDA 206162
Product Name: Lynparza (olaparib), 50 mg capsules
Indication: Ovarian Cancer
Sponsor/Applicant Name: AstraZeneca Pharmaceuticals LP

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss substantive review issues, if any, that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

CMC:

1. The proposed NMT (b) (4)% acceptance criteria for the content of the degradant, (b) (4), in olaparib capsules at end of expiry is not qualified. FDA advises that the acceptance criteria should be (b) (4)%.

2. The proposed exclusion of (b) (4) testing for (b) (4) at release of olaparib capsules is not acceptable. FDA advises that insufficient data have been provided to support the exclusion of (b) (4) testing and that all lots should be tested at release.

Reference ID: 3661540

3. As a post-marketing commitment, conduct a stability study with the process validation batches (3) with ICH primary stability testing to the submitted specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to (b) (4) months.

ADVISORY COMMITTEE MEETING

Date of AC meeting: Wednesday, June 25, 2014

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: Tuesday, June 3, 2014

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 15 minutes

CMC

- Acceptance criteria for degradant (b) (4)
- (b) (4) testing
- Stability study as post-marketing commitment

3. Information Requests – 5 minutes
4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

2824-1 Submit the progression-free survival (PFS) and 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.

PMR Schedule Milestones	Interim report (PFS analysis)	02/2016
	Trial Completion date	12/2018
	Final report Submission (OS analysis)	03/2019

Reference ID: 3661540

2824-2 Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial D0816C00010, 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 Schedule Milestones	Interim report (PFS analysis)	06/2018
	Trial Completion date	03/2020
	Final report submission (OS analysis)	06/2020

2824-3 Provide annual summaries of all cases of Acute Myelogenous Leukemia/Myelodysplastic Syndrome identified in patients treated with Lynparza (olaparib). These reports should summarize all cases identified up until that reporting date (new cases and those reported in previous years), and should include patients treated with Lynparza on clinical trials and outside of clinical trials (including spontaneous safety reports).

PMR Schedule Milestones	Annual Summary #1	12/2015
	Annual Summary #2	12/2016
	Annual Summary #3	12/2017
	Annual Summary #4	12/2018
	Annual Summary #5	12/2019
	Final Report Submission	06/2020

2824-4 Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase 1 Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment".

PMR Schedule Milestones	Interim report (planned primary PK analysis)	09/2015
	Trial completion	08/2016
	Final Report Submission	11/2016

Reference ID: 3661540

2824-5 Submit the final report for trial D0816C00005 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, Phase 1 Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment."

PMR Schedule Milestones	Interim report (planned primary PK analysis)	09/2015
	Trial Completion date	08/2016
	Final Report Submission	11/2016

***Note:* The following PMC 2824-6 is currently under review by AstraZeneca**.

2824-6 Conduct a stability study with the process validation batches (minimum of 3): ICH primary stability testing to the submitted NDA specifications (acceptance criteria, analytical method) for the commercial product, including (b) (4) up to end of expiry.

PMC Schedule Milestones	Study Completion	AZ to propose
	Final Report Submission	AZ to propose
	Other: Data Submission	At each time point

AstraZeneca is to provide a proposal of the month and year for each milestone above as well as for each time point data is to be submitted.

5. Review Plans – 15 minutes

FDA is completing primary reviews, after which the cross-disciplinary, Divisional and signatory authority reviews will be completed.

6. Wrap-up and Action Items – 5 minutes

Reference ID: 3661540

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/s/

AMNA IBRAHIM
11/20/2014