

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209115Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 209115

SUPPL # N/A

HFD # 150

Trade Name RUBRACA™ Tablets, 200 mg and 300 mg

Generic Name (rucaparib)

Applicant Name Clovis Oncology, Inc.

Approval Date, If Known December 19, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

N/A

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:

N/A

c) 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

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

YES ☐ NO ☒

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

N/A

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

N/A

- 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 ☐

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"):

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 #2

YES ☐ ! NO ☐

! Explain:

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: Kim J. Robertson
Title: Regulatory Health Project Manager
Date: December 12, 2016

Name of Division Director signing form: Geoffrey Kim, MD
Title: Director, Division of Oncology Products 1

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/

KIM J ROBERTSON
12/22/2016

GEOFFREY S KIM
12/28/2016

DEBARMENT CERTIFICATION

Clovis Oncology, Inc. (Clovis) hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Jeri Beltman, PhD

Digitally signed by Jeri Beltman, PhD
DN: cn=Jeri Beltman, PhD, o=Clovis Oncology, ou,
email=jbeltman@clovisoncology.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2016.06.17 14:29:07 -07'00'

Senior Director, Regulatory Affairs
Clovis Oncology, Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209115	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Rubraca™ Established/Proper Name: rucaparib Dosage Form: Tablet, 200 mg and 300 mg		Applicant: Clovis Oncology, Inc. Agent for Applicant (if applicable): N/A
RPM: Kim J. Robertson		Division: Division of Oncology Products 1
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>February 23, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☒ Received - November 21, 2016
❖ Application Characteristics ³		

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

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

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

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME- Type 1
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments: N/A

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

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) December 19, 2016
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included November 22, 2016
• Original applicant-proposed labeling	☒ Included June 23, 2016
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included November 22, 2016
• Original applicant-proposed labeling	☒ Included June 23, 2016
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	☒ Included June 23, 2016 November 7, 2016 (final carton and container-applicant submitted)
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s): Conditional Acceptance	August 2, 2016 March 3, 2016
• Review(s) :	February 26, 2016
❖ Labeling reviews (indicate dates of reviews)	RPM: ☐ None September 1, 2016 DMEPA: ☒ September 29, 2016 None DMPP/PLT (DRISK): November 7, 2016 ☐ None OPDP: ☒ November 7, 2016 None SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Other: ☒ Secondary Labeling; Assoc. Dir of Labeling- November 25, 2016 None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	August 22, 2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ December 28, 2016

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

❖ 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 - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC N/A If PeRC review not necessary, explain:	This drug was granted Orphan Designation and is therefore exempt from PREA
❖ Breakthrough Therapy Designation	☒
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted; April 3, 2015
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	March 25, 2015
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	June 29, 2016 (2) June 30, 2016 July 13, 2016 July 28, 2016 (2) August 3, 2016 August 4, 2016 August 11, 2016 August 16, 2016 August 18, 2016 August 19, 2016 August 22, 2016 August 30, 2016 (2) September 8, 2016 (2) September 9, 2016 September 14, 2016 (2) September 16, 2016 September 20, 2016 September 28, 2016 (2) September 29, 2016 (2) October 7, 2016 October 11, 2016 October 18, 2016 (3) October 20, 2016 October 21, 2016 October 25, 2016 October 26, 2016 (2)

	October 27, 2016 (2) October 28, 2016 November 1, 2016 November 2, 2016 (2) November 10, 2016 November 14, 2016 November 17, 2016 November 22, 2016 (4) November 28, 2016 (2) November 30, 2016 (2) December 1, 2016 December 12, 2016 December 13, 2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
• Pre-NDA/BLA meeting	☐ No mtg April 4, 2016 CMC - April 20, 2016
• EOP2 meeting	☐ No mtg November 4, 2014
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A October 20, 2016
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A November 10, 2016
• Other milestone meetings • Type C guidance – development program Type C guidance - collecting PRO data Type C guidance - methodology & analyses applied to phase 3 studies Type B – Multi-disciplinary breakthrough therapy meeting Type B – CMC breakthrough therapy meeting Type B – pre NDA meeting Type B – pre NDA (CMC) meeting	August 3, 2012 December 14, 2012 May 6, 2014 August 20, 2015 November 2, 2015 April 4, 2016 Cancelled – prelim minutes sent
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None December 15, 2016
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None December 15, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None See Office Director Review December 15, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 4 PMRs; 2 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review See Office Director Review December 15, 2016
• Clinical review(s) (<i>indicate date for each review</i>)	See Office Director Review December 15, 2016

• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	See Clinical Section of Office Director Review December 15, 2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☐ None QT-IRT; October 7, 2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	N/A November 17, 2016 ☐ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested October 14, 2016; October 31, 2016; November 8, 2016 (2) November 28, 2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☐ None See Office Director Review December 15, 2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None See Office Director Review December 15, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None See Office Director Review December 15, 2016
❖ 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 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☐ None November 18, 2016
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☐ None DS Review: November 15, 2016; DP Review: November 17, 2016 Biopharmaceutical Review: November 2, 2016 Process Review: November 16, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	November 16, 2016
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, December 13, 2016 1:26 PM
To: 'Jeri Beltman'
Subject: RE: Rubraca Labeling

You are most welcome.
~K

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, December 13, 2016 1:24 PM
To: Robertson, Kim
Subject: RE: Rubraca Labeling

Dear Kim-
Thank you very much for this confirmation. Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, December 13, 2016 10:23 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: FW: Rubraca Labeling

Dear Jeri:

I was notified by my DMEPA colleagues that they do not have any further comments and/or recommendations for Clovis' Rubraca Carton and Container.
We therefore, consider the Rubraca USPI (submitted November 22, 2016) and Carton and Container presentations (submitted November 7, 2016) final.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1

Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Robertson, Kim
Sent: Monday, December 12, 2016 4:52 PM
To: 'Jeri Beltman'; Leahy, Kristine
Subject: RE: Rubraca Labeling

Dear Jeri:

DOP1's position still remains from our December 1, 2016 communication, in which we say that we have no further comments relative to the USPI. We consider the label received November 22, 2016 final. I am **confirming** with my DMEPA/CMC colleagues about whether or not they deem the carton and container components submitted on November 7, 2016 final. I have received feedback from my CMC colleagues that they have no additional comments for the C&C and the PI and it is final from their perspective; HOWEVER, DMEPA has not weighed in. When we receive feedback/confirmation from DMEPA, either myself, or Kristine will notify you.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: (b) (4) 4:05 PM
To: Robertson, Kim; Leahy, Kristine
Subject: Rubraca Labeling

Dear Kim & Kristine-

(b) (4)

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

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/s/

KIM J ROBERTSON
12/13/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, December 12, 2016 4:52 PM
To: 'Jeri Beltman'; Leahy, Kristine
Subject: RE: Rubraca Labeling

Dear Jeri:

DOP1's position still remains from our December 1, 2016 communication, in which we say that we have no further comments relative to the USPI. We consider the label received November 22, 2016 final. I am **confirming** with my DMEPA/CMC colleagues about whether or not they deem the carton and container components submitted on November 7, 2016 final. I have received feedback from my CMC colleagues that they have no additional comments for the C&C and the PI and it is final from their perspective; HOWEVER, DMEPA has not weighed in. When we receive feedback/confirmation from DMEPA, either myself, or Kristine will notify you.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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U.S. Food and Drug Administration
Tel: 301-796-1441
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From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, December 12, 2016 4:05 PM
To: Robertson, Kim; Leahy, Kristine
Subject: Rubraca Labeling

Dear Kim & Kristine-

(b) (4)

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
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www.clovisoncology.com

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/s/

KIM J ROBERTSON
12/12/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, December 01, 2016 12:02 PM
To: 'Jeri Beltman'; Leahy, Kristine
Subject: RE: PLAIR for Rubraca NDA 209,115 - Granted NDA 209115, Rucaparib 300mg tablets

Dear Jeri:

I have received feedback today that the PLAIR is being processed. I anticipate that you/Clovis will be contacted from someone from CDER-OC-PLAIR regarding that matter.

Relative to the labeling, the USPI version of labeling submitted on November 22, 2016 is deemed the final version of labeling and is acceptable. We have no further comments Jeri.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Thursday, December 01, 2016 11:05 AM
To: Robertson, Kim; Leahy, Kristine
Subject: FW: PLAIR for Rubraca NDA 209,115 - Granted NDA 209115, Rucaparib 300mg tablets

Dear Kim and Kristine-

Notification of the PLAIR grant is being provided to you for your information and records. Clovis would very much like to label stock using the USPI version submitted to NDA 209115 on November 22nd as sequence number 0057. Please confirm that no further comments are expected and the use of this USPI version for labeling of product to be shipped under the PLAIR is acceptable.

Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: CDER-OC-PLAIR [<mailto:CDER-OC-PLAIR@fda.hhs.gov>]
Sent: Thursday, December 01, 2016 5:40 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: DIOP Plair <DIOPPlair@fda.hhs.gov>; CDER-OC-PLAIR <CDER-OC-PLAIR@fda.hhs.gov>
Subject: FW: PLAIR for Rubraca NDA 209,115 - Granted NDA 209115, Rucaparib 300mg tablets

At this time, FDA, Center for Drug Evaluation and Research (CDER) will allow the importation of NDA 209115, Rucaparib 300mg tablets, under the Pre-launch Activities importation Request (PLAIR). Please make sure that your firm is registered and once the application has been approved you must list your drug product before commercial distribution.

Prior to importing, please provide in advance to ORA/DIO (DIOPPLAIR@fda.hhs.gov), the entry number involved that your company is importing under this PLAIR. Please keep in mind that the actual amount of product imported into the US must match, as well as any other information, with what you stated in the PLAIR request. Otherwise, an amended PLAIR must be submitted to CDER-OC-PLAIR@fda.hhs.gov for an "admissibility recommendation" which supersedes previous PLAIR(s) submitted. You may make the changes on the initial PLAIR request, however explain all changes made and identify the document as an "amendment" to differentiate it from the initial PLAIR request.

Once your application has been approved, please provide us (CDER-OC-PLAIR and ORA/DIO) with a copy of the approval letter.

Note: only one import entry ready for launching regardless of the quantity, batches or lot numbers offered for imports will be acceptable.

Thanks,
CDER-OC-PLAIR

From: CDER-OC-PLAIR
Sent: Thursday, December 01, 2016 8:32 AM
To: 'Jeri Beltman'
Cc: CDER-OC-PLAIR
Subject: RE: PLAIR for Rubraca NDA 209,115

Dear Jeri, we track our PLAIR submissions by the application number. We do not use "commas" in the application number. We couldn't track the PLAIR because you have included a "comma". This was why the application could not be found. For future PLAIR submissions, please do not include a "comma" in the application number in the subject line just the number as a whole.

Thanks,
CDER-OC-PLAIR

From: CDER-OC-PLAIR
Sent: Thursday, December 01, 2016 8:26 AM
To: Jeri Beltman
Subject: RE: PLAIR for Rubraca NDA 209,115

Dear Jeri, this is the first PLAIR submission we received through the PLAIR mailbox. If you have submitted your PLAIR to this mailbox on November 11, 2016 as indicated, please provide us with the email.

We will process the PLAIR.

Thanks,
CDER-OC-PLAIR

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, November 29, 2016 10:20 AM
To: CDER-OC-PLAIR
Subject: RE: PLAIR for Rubraca NDA 209,115

Dear Compliance Officer:

I submitted the attached PLAIR for NDA 209,115 on November 11th (just over 2 weeks ago). Please let me know if this has been approved and/or what by what date I can expect a decision on this.

Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Jeri Beltman
Sent: Friday, November 11, 2016 1:30 PM
To: 'CDER-OC-PLAIR@fda.hhs.gov' <CDER-OC-PLAIR@fda.hhs.gov>
Subject: PLAIR for Rubraca NDA 209,115

Dear Compliance officer:

Please find attached the PLAIR for Rubraca. NDA 209,115 (for Rubraca) is currently under priority expedited review. I look forward to your favorable approval of this request.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

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/s/

KIM J ROBERTSON
12/01/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, November 30, 2016 12:31 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: FW: SPL procedural questions

A typo/grammar correction.....

From: Robertson, Kim
Sent: Wednesday, November 30, 2016 12:17 PM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: SPL procedural questions

Dear Jeri:

As for the SPL process, I would suggest that you contact spl@fda.hhs.gov , or esub@cder.fda.gov . This is ~~there~~ **their** area of expertise and I'm certain that they can assist you further with your understanding as to what it is Clovis would need to submit relative to SPL. Since all promotional materials have been submitted and received by our Document Room (thank you for the notification), I presume that Clovis included its 300 mg sample package, if that is something Clovis intends to use in the first 120 days following marketing approval (i.e., your launch campaign).

Lastly, with regards to your PLAIR, I have reached out to the same CDER-OC-PLAIR group that I'm sure you e-mailed, as well as 2 other colleagues that may be of assistance. I have asked them to please look into this and to follow-up with you with any information they may have. Please keep me posted on this matter, in case they circumvent me and respond directly to you.

-Kim

Kim J. Robertson
Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, November 29, 2016 7:21 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: SPL procedural questions

Dear Kim-

We will be using an external SPL vendor to produce the final SPL. While, we feel confident in our vendor, we have a few questions relating to the SPL submission process. These are as follows.

Our reading of the guidance documents relating to structure product labeling suggests that within 14 days of approval, Clovis should :

- submit to NDA section 14.2.2 (final carton or container labels), a PDF of the container labels for the 200 mg bottles and for the 300 mg bottles. It is unclear to us if the label for the 300 mg sample packs is also required?
- submit to NDA section 14.2.2 (final package insert), the word version of the final package insert text
- submit to NDA section 1.14.2.3 (final labeling text), the SPL that includes the final package insert text as well as the container labels
- submit to the office of the commissioner the SPL that includes the final package insert text as well as the container labels, so that it can then be posted to drugs@fda and to Daily Med.

Please confirm that our understanding of what is required, as outlined above, is correct.

Also, you should be aware that a 6 box package of promotional materials, as required by OPDP, was received by the FDA document room on Monday November 21st.

Lastly, as you are aware Clovis submitted a PLAIR on Friday November 11th. Although 10 business days have elapsed, we have not received a response to this request. I attempted to follow up by e-mail today, but also got no response. If there is a mechanism for you to follow up internally at FDA that would be greatly appreciated.

Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

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/s/

KIM J ROBERTSON
11/30/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, November 28, 2016 11:17 AM
To: 'Hanna Cho'
Cc: Jeri Beltman
Subject: RE: NDA 209115; PMR/PMC Templates Update

Good morning Hanna/Jeri:

I hope you ladies had a wonderful Thanksgiving Holiday.

Relative to your question seeking clarification of "Other" for the following clinical pharmacology PMR:

PMR: Conduct a dedicated PK (b) (4) in patients with moderate hepatic impairment to determine the appropriate starting dose in patients with moderate hepatic impairment.

Final Report Submission: MM/DD/YYYY

Other: MM/DD/YYYY

I was notified that Clovis is to disregard the "Other". A proposed date for Final Report Submission will be sufficient. Please provide a date for that by **Tuesday, November 29, 2019, 4:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

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kim.robertson@fda.hhs.gov



From: Hanna Cho [mailto:hcho@clovisoncology.com]
Sent: Wednesday, November 23, 2016 1:34 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Kim,

Your update is highly appreciated.

Kind regards,
Hanna

Hanna H. Cho, PhD, RAC
Manager, Regulatory Affairs
Clovis Oncology, Inc. | San Francisco, CA, USA
Office +1.415.409.5491 | Mobile (b) (6) | hcho@clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, November 23, 2016 10:27 AM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hello Hanna:

I just wanted to let you know that I still have your question on my radar. I am still awaiting word from the requesting reviewer and I believe there was one other person he was going to get confirmation from. Again, as soon as I hear from him, I will update you.

-Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Tuesday, November 22, 2016 6:26 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115; PMR/PMC Templates Update

Thank you, Kim!
Hanna

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, November 22, 2016 3:25 PM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hanna, I have conveyed your question to the requesting clinpharm reviewer and as soon as I receive a response from him, I will absolutely let you know.

-K

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Tuesday, November 22, 2016 6:13 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115; PMR/PMC Templates Update

Dear Kim,

Clovis acknowledges the receipt of this request. Would you advise on what "Other:" means under PMR for PK study in patients with moderate hepatic impairment?

Thank you,
Hanna

Hanna H. Cho, PhD, RAC
Manager, Regulatory Affairs
Clovis Oncology, Inc. | San Francisco, CA, USA
Office +1.415.409.5491 | Mobile (b) (6) | hcho@clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, November 22, 2016 3:03 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update
Importance: High

Hi Jeri:

To circle back to your question re: the Clinical Pharmacology PMR/PMC Milestones, please see the following and propose dates :

PMC: Submit the final (b) (4) report of ongoing mass balance trial CO-338-045.
Final Report Submission: MM/DD/YYYY

PMR: Complete the ongoing drug-drug interaction trial CO-338-044 and submit the final study report.
Final Report Submission: MM/DD/YYYY

PMR: Conduct a dedicated PK (b) (4) in patients with moderate hepatic impairment to determine the appropriate starting dose in patients with moderate hepatic impairment.
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY

*Note—the actual template/worksheet was purposely omitted. The important matters to address have been extracted above. Please provide us with your proposed dates by **Monday, November 28, 2016, 4:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, November 21, 2016 4:17 PM
To: Robertson, Kim; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

Dear Kim-

Thank you for the clarification regarding the required protocol. As provided today both to the NDA and as a courtesy copy, Clovis proposes that the protocol will be submitted to FDA by June 2017. Based on the additional information you provided below, we will need to secure a diagnostic partner which is still ongoing. Thus the date of June 2017 provided to you earlier today remains appropriate.

Clovis is anticipating the 3 Clinical Pharmacology PMC/PMR worksheets sometime soon. If possible, please let me know when Clovis may expect these.

Regards, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, November 21, 2016 1:05 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>; Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Jeri/Hanna:

Relative to the clarification you were seeking, please see the following:

- A protocol which outlines your analysis plan, including statistical analysis plan and your approach to bridging results from the new test with prior results, should be submitted for FDA review. If all samples are existing, as you state, the protocol would not need to describe collection of new samples.

Regards,

Kim

Kim J. Robertson

Regulatory Health Project Manager

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From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Friday, November 18, 2016 2:18 PM
To: Robertson, Kim; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Kim-

Regarding the BRCA PMC, FDA is asking that we submit a protocol . Please clarify what FDA is looking for. Clovis plans to use existing samples, so no clinical protocol will be required to enable sample collection. Is FDA asking for an statistical analysis plan?

Clarification would be appreciated.

Thanks, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, November 18, 2016 7:58 AM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: NDA 209115; PMR/PMC Templates Update

Hello Hanna:

Please see the attached document, as we have a few edits we need Clovis to review. We are still in need of some additional information as well.

Please review and send this back to us no later than **Monday, November 21, 2016, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

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/s/

KIM J ROBERTSON
11/28/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, November 28, 2016 5:45 PM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib ---IR re: Container Labels

Excellent. Thank you Jeri.
Kim

Kim J. Robertson

Regulatory Health Project Manager

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kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, November 28, 2016 5:37 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: Re: NDA 209115; rucaparib ---IR re: Container Labels

Dear Kim

Yes, I can confirm that the label submitted to you on November 7th is being printed for commercial use. Regards, Jeri

On Nov 28, 2016, at 2:09 PM, Robertson, Kim <Kim.Robertson@fda.hhs.gov> wrote:

Hi Jeri:

Would you please confirm for me that the container labeling that Clovis, Inc. submitted on November 7, 2016 for rucaparib, in response to a CMC Information Request from Kristine Leahy, is the container labeling to be used as **final labeling for Rubraca**, provided the application is approved?

Kim

Kim J. Robertson

Regulatory Health Project Manager

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KIM J ROBERTSON
11/28/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, November 21, 2016 4:42 PM
To: 'Jeri Beltman'; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Jeri:

I believe my clinpharm colleagues have left for the evening, but I have asked them about the PMR/PMC information and as soon as I receive word from them, I will let Clovis know.

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, November 21, 2016 4:17 PM
To: Robertson, Kim; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

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Clovis is anticipating the 3 Clinical Pharmacology PMC/PMR worksheets sometime soon. If possible, please let me know when Clovis may expect these.

Regards, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, November 21, 2016 1:05 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>; Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Jeri/Hanna:

Relative to the clarification you were seeking, please see the following:

- A protocol which outlines your analysis plan, including statistical analysis plan and your approach to bridging results from the new test with prior results, should be submitted for FDA review. If all samples are existing, as you state, the protocol would not need to describe collection of new samples.

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Clarification would be appreciated.

Thanks, Jeri

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Sent: Friday, November 18, 2016 7:58 AM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: NDA 209115; PMR/PMC Templates Update

Hello Hanna:

Please see the attached document, as we have a few edits we need Clovis to review. We are still in need of some additional information as well.

Please review and send this back to us no later than **Monday, November 21, 2016, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

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KIM J ROBERTSON
11/22/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 22, 2016 12:10 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib USPI---Additional FDA Revisions
Attachments: 22November2016 Rucaparib USPI with Additional FDA Edits.docx

Importance: High

Hello Jeri:

We have a few additional revisions that we made to Clovis' rucaparib USPI. Please review. We need a return USPI no later than **Friday, November 25, 2016, 2:00pm, EST**, with either Clovis' concurrence, or comments.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
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KIM J ROBERTSON
11/22/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 22, 2016 12:10 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib USPI---Additional FDA Revisions
Attachments: 22November2016 Rucaparib USPI with Additional FDA Edits.docx

Importance: High

Hello Jeri:

We have a few additional revisions that we made to Clovis' rucaparib USPI. Please review. We need a return USPI no later than **Friday, November 25, 2016, 2:00pm, EST**, with either Clovis' concurrence, or comments.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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/s/

KIM J ROBERTSON
11/22/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 22, 2016 6:03 PM
To: 'Jeri Beltman'
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: RE: NDA 209115; PMR/PMC Templates Update

Importance: High

Hi Jeri:

To circle back to your question re: the Clinical Pharmacology PMR/PMC Milestones, please see the following and propose dates :

PMC: Submit the final (b) (4) report of ongoing mass balance trial CO-338-045.
Final Report Submission: MM/DD/YYYY

PMR: Complete the ongoing drug-drug interaction trial CO-338-044 and submit the final study report.
Final Report Submission: MM/DD/YYYY

PMR: Conduct a dedicated PK (b) (4) in patients with moderate hepatic impairment to determine the appropriate starting dose in patients with moderate hepatic impairment.
Final Report Submission: MM/DD/YYYY
Other: MM/DD/YYYY

*Note—the actual template/worksheet was purposely omitted. The important matters to address have been extracted above. Please provide us with your proposed dates by **Monday, November 28, 2016, 4:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [mailto:jbeltman@clovisoncology.com]
Sent: Monday, November 21, 2016 4:17 PM
To: Robertson, Kim; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

Dear Kim-

Thank you for the clarification regarding the required protocol. As provided today both to the NDA and as a courtesy copy, Clovis proposes that the protocol will be submitted to FDA by June 2017. Based on the additional information you provided below, we will need to secure a diagnostic partner which is still ongoing. Thus the date of June 2017 provided to you earlier today remains appropriate.

Clovis is anticipating the 3 Clinical Pharmacology PMC/PMR worksheets sometime soon. If possible, please let me know when Clovis may expect these.

Regards, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, November 21, 2016 1:05 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>; Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Jeri/Hanna:

Relative to the clarification you were seeking, please see the following:

- A protocol which outlines your analysis plan, including statistical analysis plan and your approach to bridging results from the new test with prior results, should be submitted for FDA review. If all samples are existing, as you state, the protocol would not need to describe collection of new samples.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Friday, November 18, 2016 2:18 PM
To: Robertson, Kim; Hanna Cho
Subject: RE: NDA 209115; PMR/PMC Templates Update

Hi Kim-

Regarding the BRCA PMC, FDA is asking that we submit a protocol. Please clarify what FDA is looking for. Clovis plans to use existing samples, so no clinical protocol will be required to enable sample collection. Is FDA asking for an statistical analysis plan?

Clarification would be appreciated.

Thanks, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, November 18, 2016 7:58 AM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: NDA 209115; PMR/PMC Templates Update

Hello Hanna:

Please see the attached document, as we have a few edits we need Clovis to review. We are still in need of some additional information as well.

Please review and send this back to us no later than **Monday, November 21, 2016, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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

/s/

KIM J ROBERTSON
11/22/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, November 17, 2016 4:04 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib-- 17November16 rucaparib USPI with FDA Revisions and Comments
Attachments: 17November2016 Rucaparib USPI wFDA Revisions and Comments.docx
Importance: High

Hello Jeri:

Please see the attached Word .doc as it is Clovis' rucaparib USPI with FDA Revisions and Comments. Please review and provide us with a return label with either Clovis' acceptance of the revisions, or any additional revisions comments/concerns Clovis may have, by **Monday, November 21, 2016, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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

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

/s/

KIM J ROBERTSON
11/17/2016



NDA 209115

MID-CYCLE COMMUNICATION

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rucaparib, 200 mg and 300 mg tablet.

We also refer to the teleconference between representatives of your firm and the FDA on October 20, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



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

MID-CYCLE COMMUNICATION

Meeting Date and Time: Thursday, October 20, 2016; 1:00pm – 2:00pm EST

Application Number: NDA #209115
Product Name: rucaparib
Indication: **Advanced ovarian cancer**
Applicant Name: Clovis, Inc.

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Cross Discipline Team Leader and Acting Associate Director, DOP1
Sanjeeve Balasubramaniam, MD, PhD, Clinical Reviewer, DOP1
Sara Horton, MD, Clinical Reviewer, DOP1
Laura Fernandes, PhD, Biometrics Reviewer, OBP
Shenghui Tang, PhD, Biometrics Team Leader, OBP
Jinzhong Liu, PhD, Clinical Pharmacology Reviewer, DPM
Sarah Schrieber, PharmD, Clinical Pharmacology Reviewer, DCP5
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP5
Chao Liu, PharmD, Pharmacometrics Reviewer, DPM
Jingyu (Jerry) Yu, PhD, Pharmacometrics Team Leader, DPM
Haw-Jyh (Brian) Chiu, PhD, Nonclinical Reviewer, DHOT
Todd Palmby, PhD, Nonclinical Team Leader, DHOT
Monica Cooper, PhD, Drug Substance Reviewer, OPQ
Xing Wang, PhD, Drug Product Reviewer, OPQ
Xiao Chen, PhD, Acting CMC Team Leader, OPQ
Rosane Charlab-Orbach, PhD, Genomics Team Leader, GTTG
Kim J. Robertson, Regulatory Health Project Manager, DOP1

APPLICANT ATTENDEES

Jeri Beltman, PhD, Senior Director, Regulatory Affairs
Hanna Cho, PhD, Manager, Regulatory Affairs
Jeff Etter, PhD, Vice President, Pharmaceutical Development
Heidi Giordano, MA, MBA, Vice President, Clinical Science
Jeff Isaacson, PhD, Vice President, Biostatistics & Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lara Maloney, Director, Clinical Science

Lindsey Rolfe, MBChB, Chief Medical Officer & Executive Vice President
Andrew Simmons, PhD, Senior Director, Translational Medicine
Jim Xiao, PhD, Associate Director, Clinical & Nonclinical Pharmacology

Eastern Research Group Attendees:

(b) (6), Eastern Research Group, Inc.

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

We currently do not have any significant review issues that could preclude the approval of this application.

Please note that our review is ongoing and we will have post-marketing requirements and commitments.

3.0 INFORMATION REQUESTS

Outstanding/new information requests at the time of the midcycle meeting (October 20, 2016) included:

Clinical:

1. An information request was sent on October 12, 2016, which revolves around discrepancies between Investigator and IRR assessments and exposure-response relationships, and further justification of accelerated approval referencing comparable available treatments. We ask that you compare exposure tumor dynamics for INV and IRR.
2. Identify the location in the submission or provide further details regarding the specific type of arrhythmia that was experienced by patient 16005-202 in study CO-338-017 (i.e., Vtach, bradycardia, afib).
3. Identify the location in the submission or provide an additional summary table of TEAEs by age for the following groups of patients (as columns) patients <65 years,

≥65 to <75 years, ≥75 years, and ≥65 yrs, in the ovarian cancer safety population (N=378), by the following rows:

- Patients with one or more TEAE
- Patient with one or more Serious TEAE
- Patients with one or more TEAE of grade 3 or higher
- Patient with one or more TEAE leading to death
- Patients with one or more TEAE leading to dose reduction
- Patients with one or more TEAE leading to dose interruption
- Patients with TEAE leading to discontinuation

Clinical Pharmacology/Pharmacometrics:

4. In the PPK analysis, the concomitant drugs were treated as a time independent covariates. The timing of the co-administration of other drugs should be considered in the analysis. Please clarify if the timing of administration of concomitant drugs was available, and if so, please evaluate the effect of concomitant drugs on rucaparib PK by treating them as time-varying covariates in PPK analysis.
5. In the “Addendum to Exposure-Response Analysis”, doses administered after the time of confirmed response or progressive diseases were not included for the calculations of the exposure for both investigator and IRR response. Please provide the time to the last dose used to generate these exposure metrics for each subject (both investigator and IRR assessed ORR).

CMC:

Drug Process

(b) (4)

(b) (4)

10. You have stated that section 3.2.P of your application would be updated in response to previous process related information requests, but you have not updated section 3.2.P. Please update section 3.2.P to agree with your responses provided on 09/23/2016 and your responses to this information request.

(b) (4)

Biopharmaceutics

12. The proposed dissolution acceptance criterion of “Q = (b) (4)” is not acceptable, and the dissolution data provided support a tighter acceptance criterion of “Q = (b) (4) at 15 min”. Implement the recommended dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

Drug Substance and Drug Product

13. Submit the full report for the forced degradation study described in your responses to IR-20160830a (item #2) and IR-20160906a (item #1), including raw chromatograms, tabular analytical results and peak purity plots, etc.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

All major safety concerns can be addressed through review of the submission and the responses to our information requests.

5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for November 10, 2016; 1:00pm- 2:00pm, Eastern Standard Time. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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

/s/

GEOFFREY S KIM
11/15/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, November 14, 2016 4:56 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: FW: NDA 209115; rucaparib IR
Attachments: Rucaparib NDA 209115 PMR-PMC Template_germline test.doc; Rucaparib NDA 209115 PMRTemplate ARIEL4.doc; Rucaparib NDA 209115 PMRTemplate ARIEL3.doc

Importance: High

Jeri:

We need to have a response relative to these milestone dates by **Thursday, November 17, 4:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Robertson, Kim
Sent: Monday, November 14, 2016 4:53 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib IR
Importance: High

Hi Jeri:

Please review the following PMR-PMC templates and provide milestone dates for each of the templates.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration*

Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

PMR/PMC Development Template

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

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

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

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

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

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

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

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Required

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

Continuation of Question 4

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

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)
Study to demonstrate the analytical and clinical validity of a germline BRCA mutation test
-

Agreed upon:

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

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

PMR Description: Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial CO-338-014 entitled, "Phase 3 Study of Rucaparib as Switch Maintenance After Platinum in Relapsed High Grade Serous and Endometrioid Ovarian Cancer" (ARIEL3).

PMR/PMC Schedule Milestones:	Final Protocol Submission (ARIEL3):	<u>Submitted 09/09/2013</u>
	Trial Completion:	<u>1/2017</u>
	Final Report Submission:	<u>7/2017</u>

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

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

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

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

ARIEL3, the ongoing randomized, double-blind, placebo-controlled, multi-center trial to assess the efficacy of rucaparib maintenance monotherapy in relapsed high-grade serous ovarian cancer patients (b) (4) high-grade endometroid cancer with BRCA mutations in tumor tissue (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 to platinum-based chemotherapy. This trial will establish the efficacy of rucaparib in maintenance treatment, an earlier line of therapy than the current accelerated approval.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?

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

☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Randomized, double-blind, placebo-controlled, multi-center trial to assess the efficacy of rucaparib maintenance monotherapy in improving PFS and/or OS in relapsed high-grade serous ovarian cancer (b) (4) or high-grade endometroid cancer with BRCA mutations in tumor tissue (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 to platinum-based chemotherapy (study CO-338-014 , ARIEL3).

Required

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

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/ #	209115
Product Name:	<u>Rubraca (Rucaparib) 300 mg tablet, 200 mg tablet</u>
PMR Description:	<u>Submit the progression-free survival (PFS) and overall survival (OS) analyses with datasets from clinical trial CO-338-043 entitled "A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, BRCA Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer," (ARIEL4).</u>
PMR Schedule Milestones:	Final Protocol Submission (ARIEL4): <u>Submitted 06/20/2016</u>
	Trial Completion: <u>4/2022</u>
	Final Report Submission: <u>10/2022</u>

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

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

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

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

ARIEL4 is a planned multicenter, open-label, randomized trial of rucaparib vs chemotherapy in patients with BRCA-mutated or (b) (4) relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. This trial will establish the superiority of single-agent rucaparib over conventional third-line chemotherapy.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Multicenter, open-label, randomized trial of rucaparib vs chemotherapy in patients with BRCA-mutated or (b) (4) relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (study CO-338-043, ARIEL4) to establish the superiority of rucaparib over physician's choice chemotherapy in this patient population (study CO-338-043, ARIEL4).

Required

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

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

KIM J ROBERTSON
11/14/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 08, 2016 6:43 PM
To: 'Jeri Beltman'
Subject: RE: Clovis LCM
Attachments: Final Late-Cycle Meeting Background Package NDA 209115 Rubraca (rucaparib) (COR-MEET-07).pdf

Importance: High

Hi Jeri:

Please see the background information we have prepared for the Late Cycle Meeting slated for Thursday, November 10, 2016. Please note that the team has been apprised of the topics of possible interest to Clovis for the teleconference meeting. Perhaps this document may answer some questions for Clovis.

Some of Clovis' questions may be best answered during the t-con; other questions you asked (i.e., Is it possible to know are the individual discipline reviews complete, or what is the schedule? Is there a schedule for the primary review to be completed and a plan for the higher level reviews?) are not providing guidance per se, but are more our internal specifics/milestones that we generally do not disclose to our sponsors and/or applicants.

It is our intent to provide Clovis with any additional PI comments by tomorrow, November 9, 2016. If we have any substantive matters to discuss at this juncture, I assure you that the concerned disciplines will mention them at the time of the meeting and if need be, as the review process continues.

The MCM minutes will be forthcoming very soon.

Please see the following call-in information re: the LCM:

Teleconference information

1. Dial: Local: (b) (4)
Toll free: (b) (4)
 2. Follow the instructions that you hear on the phone.
- MeetingPlace Meeting ID: (b) (4)

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

*Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, November 08, 2016 11:00 AM
To: Robertson, Kim
Subject: Clovis LCM

Dear Kim-

Based on our phone call yesterday, I am left with the impression that FDA may not consider that there sufficient topics to warrant a F2F meeting, or that the timing is not quite right for the topics that merit discussion. We are looking to FDA for guidance regarding the F2F versus teleconference option as well as the timing for the meeting itself.

We are looking to you for guidance because we do not know what outstanding or critical review issues remain. At the time of the MCM meeting no significant review issues were raised. Although Clovis does not expect a formal MCM communication until 30 days after the meeting (i.e., Nov. 20th), we have no information regarding the contents of this communication to guide us. As such, we would like to point out that currently we do not know where we stand in the review process and this is why F2F discussion or formal teleconference would be useful.

For instance, Clovis is seeking clarity regarding several topics for which we understand information should be available at this point in the review. We further understand that although it is not possible to communicate the official action until the review is complete, some guidance to the sponsor could be provided concerning the following:

- Is it possible to know are the individual discipline reviews complete, or what is the schedule?
- Have the inspection reports been received and are there any issues?
- When can we expect the next round of PI comments?
- Is there a schedule for the primary review to be completed and a plan for the higher level reviews?

In addition to the specific agenda questions provided yesterday, Clovis hopes you find the above bulleted comments appropriate for inclusion at the late cycle meeting.

I look forward to your feedback as early as possible today. In particular, if FDA is still considering a teleconference in lieu of a F2F meeting, then the Clovis team will need time to alter our travel plans. I will give you a call to discuss the LMC plans (F2F vs teleconference, as well as the agenda) at 9:00 am PST / 12:00 (noon) EST.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com



NDA 209115

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rubraca (rucaparib), 200 mg and 300 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 10, 2016.
Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 10, 2016; 1:00pm-2:00pm, EST
Meeting Location: WO Bldg. #22; Conf. Room 4201 (teleconference)

Application Number: NDA # 209115
Product Name: Rubraca® (rucaparib)
Indication: Ovarian Cancer
Sponsor/Applicant Name: Clovis, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), 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.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, 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:
Clinical PMRs and PMCs
Clinical Pharmacology studies

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Kim J. Robertson/Julia Beaver, MD)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion:

- Clinical PMR: Submit the results of ARIEL 3 and ARIEL 4 (update on status)
- Clinical PMC: Germline BRCA test
- Clinical Pharmacology PMR: Hepatic impairment study (Moderate); (b) (4) drug-drug interaction study
- Clinical Pharmacology: Status of the Mass Balance Study; characterization of metabolites

3. Discussion of Minor Review Issues – 10 minutes

- Labeling Concerns from the Applicant

- (b) (4)

4. Review Plans – 5 minutes

The Division anticipates it will continue its expedited review of the application, barring no unexpected shift in work priorities or team staffing. If unexpected significant issues arise during the course of the review, the review plan will default to normal priority review timelines.

5. Wrap-up and Action Items – 5 minutes (TBD following LCM)

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/s/

GEOFFREY S KIM
11/08/2016

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/s/

KIM J ROBERTSON
11/10/2016

Robertson, Kim

From: Cottrell, Christy L.
Sent: Wednesday, November 09, 2016 4:10 PM
To: Jeri Beltman
Cc: Robertson, Kim
Subject: RE: Clovis LCM
Attachments: 11-9-16 labeling to sponsor Rubraca Label.docx

Importance: High

Hi Jeri,

There is actually a very large group of people that have been invited to participate in the meeting tomorrow, many of whom will likely not attend. I think it would be better for Kim to provide you with a complete list of actual attendees after the meeting. The review team and Division management are all planning to attend.

Labeling is attached.

Christy

From: Jeri Beltman [mailto:jbeltman@clovisoncology.com]
Sent: Wednesday, November 09, 2016 11:01 AM
To: Cottrell, Christy L.
Subject: FW: Clovis LCM

Dear Christy-

I understand that Kim Robertson is out of the office today. In her absence, I wanted to acknowledge to you our receipt of the late cycle materials, and request a list of invited FDA attendees for that meeting.

Also, we are anticipating additional labeling comment ahead of Thursday's late cycle meeting. Can I expect that to come from you later today?

Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Jeri Beltman
Sent: Wednesday, November 09, 2016 7:56 AM
To: 'Robertson, Kim' <Kim.Robertson@fda.hhs.gov>
Subject: RE: Clovis LCM

Dear Kim-

Clovis acknowledges review of the LCM background information and agenda. Please provide Clovis with the list of FDA invited attendees for this meeting. Also, I anticipate that you will be providing the call-in information for Thursday.

The planned sponsor attendees are as follows:

Jeri Beltman, PhD, Senior Director, Regulatory Affairs
Hanna Cho, PhD, Manager, Regulatory Affairs
Jeff Etter, PhD, Vice President, Pharmaceutical Development
Heidi Giordano, MA, MBA, Vice President, Clinical Science
Sandra Goble, MS, Associate Director, Biostatistics
Jeff Isaacson, PhD, Vice President, Biostatistics & Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lara Maloney, Director, Clinical Science
Lindsey Rolfe, MBChB, Chief Medical Officer & Executive Vice President
Andrew Simmons, PhD, Senior Director, Translational Medicine
Jim Xiao, PhD, Associate Director, Clinical & Nonclinical Pharmacology

We look forward to receiving additional labeling comments later today, and to the teleconference on Thursday.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, November 08, 2016 3:43 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: RE: Clovis LCM
Importance: High

Hi Jeri:

Please see the background information we have prepared for the Late Cycle Meeting slated for Thursday, November 10, 2016. Please note that the team has been apprised of the topics of possible interest to Clovis for the teleconference meeting. Perhaps this document may answer some questions for Clovis.

Some of Clovis' questions may be best answered during the t-con; other questions you asked (i.e., Is it possible to know are the individual discipline reviews complete, or what is the schedule? Is there a schedule for the primary review to be completed and a plan for the higher level reviews?) are not providing guidance per se, but are more our internal specifics/milestones that we generally do not disclose to our sponsors and/or applicants.

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the concerned disciplines will mention them at the time of the meeting and if need be, as the review process continues.

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 2. Follow the instructions that you hear on the phone.
- MeetingPlace Meeting ID: (b) (4)

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, November 08, 2016 11:00 AM
To: Robertson, Kim
Subject: Clovis LCM

Dear Kim-

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In addition to the specific agenda questions provided yesterday, Clovis hopes you find the above bulleted comments appropriate for inclusion at the late cycle meeting.

I look forward to your feedback as early as possible today. In particular, if FDA is still considering a teleconference in lieu of a F2F meeting, then the Clovis team will need time to alter our travel plans. I will give you a call to discuss the LMC plans (F2F vs teleconference, as well as the agenda) at 9:00 am PST / 12:00 (noon) EST.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

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/s/

KIM J ROBERTSON
11/10/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, November 10, 2016 2:48 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; Rucaparib USPI with Additional FDA Comments
Attachments: 10November16 Rubraca USPI with Additional FDA Comments.docx

Importance: High

Hello Jeri:

Please see the attached Word .doc, as it is the rucaparib USPI. We have made an additional modification to the Indication Statement.

Please review and provide us with a return label no later than **Tuesday, November 15, 2016, 11:00am EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
11/10/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

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

Drug Substance:

1. In your response dated 07-Nov-2016 to Item 2 (from the Drug Substance Information Request dated 02-Nov-2016) regarding the inclusion of an identity test to confirm the stereochemistry of the camsylate salt (e.g., specific rotation) in the drug substance specification, you did not agree to [REDACTED] (b) (4)

Please respond to drug process comments by **COB Friday, November 11, 2016.**

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,

Kristine F. Leahy

-S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2016.11.08 11:31:59 -05'00'

Kristine Leahy, RPh.

Regulatory Business Process Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research



Kristine
Leahy

Digitally signed by Kristine Leahy
Date: 11/08/2016 11:37:00AM
GUID: 55f72bd9003d99948f388d681cbec17d

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, November 02, 2016 3:48 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib----Clinical Information Request

Hello again Jeri:

Please see the following clinical request for information relative to the rucaparib NDA:

CLINICAL INFORMATION REQUEST:

- Provide the subject ID of the patient who was identified to have endometrial cancer instead of ovarian cancer at the 60 day update.

Please provide a response to this request for information by **Thursday, November 3, 2016, 1:00p.m., EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
11/02/2016

From: Robertson, Kim
Sent: Wednesday, November 02, 2016 2:33 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib----Clinical Pharmacology Information Request

Hello Jeri:

I have returned from leave. ☺

As I attempt to re-acclimate myself with the NDA, please note below the following request for information from my clinical pharmacology discipline, relative to Clovis' NDA for rucaparib:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

Relative to the draft labeling for rucaparib:

1. Per CFR Title 21 201.57(c)(13)(i)(B), exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included in Section 12.2 of the draft label if known. Please submit the suggested edits with appropriate justification if this information is available. If this information is currently unknown, this subsection must provide a statement to state the unavailability of information.
2. For "Hepatic Impairment" in Section 12. the draft label, the current criteria for patients with mild hepatic impairment " (b) (4)
(b) (4)
(b) (4) was inconsistent with (b) (4) criteria guideline nor the definition in your summary of clinical safety (Page 83 of 88) "ALT/AST > ULN with total bilirubin ≤ ULN or any ALT/AST level with total bilirubin > 1.0-1.5 x ULN". Please provide the actual range numbers in the criteria for patients with mild hepatic impairment and patients with moderate to severe hepatic impairment.
3. For "Drug Interaction Studies" in Section 12.3 of the draft label, please clarify whether the CYP1A2 (b) (4) refers to CYP1A2 (b) (4)

Please provide responses to address these inquiries by **Friday, November 4, 2016, 2:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
11/02/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, November 01, 2016 4:27 PM
To: 'Jeri Beltman'
Cc: Hanna Cho; Robertson, Kim
Subject: RE: NDA 209115; rucaparib--USPI

Importance: High

Dear Jeri,

In reference to your inquiry below, the proposed format for your response is acceptable. Also, in reference to your request for clarification regarding FDA's proposed changes to the USPI for rucaparib sent to you on October 27, 2016, please see the FDA review team's responses below:

Question 1:

Section 5.2. FDA is recommending contraception for 6 months following the last dose of rucaparib. This is inconsistent with the IB (version 8 submitted as SN0218 to IND 109,289), which states (b) (4). Clovis is seeking additional information regarding where the 6 months came from.

FDA Response:

In general, our current approach in OHOP for contraception duration recommendations for females of reproductive potential for a genotoxic drug is as follows. Genotoxic pharmaceuticals may directly affect the embryo/fetus or may cause DNA damage in the oocytes. The period of folliculogenesis is described as 6 to 12 months (Meirow, Epstein, et al. 2001; Meirow and Schiff 2005). Exposure to a genotoxic pharmaceutical in the initial step (primordial follicles) results mainly in follicular loss (Kalich-Philosoph, Roness, et al. 2013). Any remaining damaged follicle may be further eliminated through the natural process of atresia (greater than 90 percent elimination) (Gougeon 1986). The growth and maturation phase of folliculogenesis (4 to 6 months) is most susceptible to persisting DNA damage and may potentially result in embryo-fetal malformations. Hence 6-month contraception is recommended for genotoxic pharmaceuticals. For pharmaceuticals with long half-lives (greater than or equal to 1 week) an additional five half-lives is recommended.

Since the half-life of rucaparib is short, we recommend 6 months contraception use in females of reproductive potential after the last dose.

References:

1. Meirow, D, M Epstein, et al., 2001, Administration of Cyclophosphamide at Different Stages of Follicular Maturation in Mice: Effects on Reproductive Performance and Fetal Malformations, Hum Reprod, 16:632-637.
2. Meirow, D and E Schiff, 2005, Appraisal of Chemotherapy Effects on Reproductive Outcome According to Animal Studies and Clinical Data, J Natl Cancer Inst Monogr, 34:21-25.
3. Kalich-Philosoph, L, H Roness, et al., 2013, Cyclophosphamide Triggers Follicle Activation and "Burnout"; AS101 Prevents Follicle Loss and Preserves Fertility, Sci Transl Med, 5:1-11.
4. Gougeon, A, 1986, Dynamics of Follicular Growth in the Human: A Model From Preliminary Results, Hum Reprod, 1:81-87.

Question 2:

Section 6.1. Please provide information regarding the method used and the categories of patient included for the (b) (4) % dose discontinuation rate.

FDA Response:

Using the ISS ADAE dataset, there are 64 ovarian cancer patients who discontinued treatment due to AE, 52 from an AE other than malignant progression. As malignant progression is not considered an AR, 52/377 (13.79%) patients discontinued due to AR.

Question 3:

Also, in Section 6.1 (Table 2). Please explain if FDA is regarding anemia as a group term that also includes low or decreased hemoglobin, and if FDA is regarding thrombocytopenia is a group term that that also low or decreased platelets? Or alternatively, if FDA view is that hemoglobin and platelets are captured in Table 3, and as such should not be included in Table 2?

FDA Response:

In Table 2 (AR table), anemia is a composite preferred term which includes anemia and low or decreased hemoglobin, and thrombocytopenia includes low or decreased platelets. We removed the AE preferred terms from the table that could also be considered laboratory values to avoid confusion that these are not actual laboratory values. We have therefore retained the actual laboratory value description in Table 3.

Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Jeri Beltman [mailto:jbeltman@clovisoncology.com]
Sent: Monday, October 31, 2016 2:03 PM
To: Wahby, Sakar
Cc: Hanna Cho; Robertson, Kim
Subject: RE: NDA 209115; rucaparib--USPI

Dear Sakar-

Clovis acknowledges the receipt of these labeling comments. Clovis intends to response in writing as requested. Procedurally, we intend to create a clean version by accepting all of FDA's comments. We will then include

any Clovis-proposed wording on that clean version. We intend to supply to FDA both the tracked changes version (FDA clean + Clovis comments) and well as a clean version (i.e., Clovis comments accepted). In addition, Clovis is preparing a response document in which we will respond to FDA's comments with our rationale for any proposed changes. Please confirm that the formats proposed are acceptable.

In addition, I am noting below a few of FDA's proposed changes for which Clovis is seeking additional clarity. We believe that the additional requested information will help inform the most appropriate response back to FDA.

Section 5.2. FDA is recommending contraception for 6 months following the last dose of rucaparib. This is inconsistent with the IB (version 8 submitted as SN0218 to IND 109,289), which states (b) (4) Clovis is seeking additional information regarding where the 6 months came from.

Section 6.1. Please provide information regarding the method used and the categories of patient included for the (b) (4) % dose discontinuation rate.

Also, in Section 6.1 (Table 2). Please explain if FDA is regarding anemia as a group term that also includes low or decreased hemoglobin, and if FDA is regarding thrombocytopenia is a group term that that also low or decreased platelets? Or alternatively, if FDA view is that hemoglobin and platelets are captured in Table 3, and as such should not be included in Table 2?

Thanks in advance for these additional clarifications. Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Wahby, Sakar [<mailto:Sakar.Wahby@fda.hhs.gov>]
Sent: Thursday, October 27, 2016 11:50 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>; Robertson, Kim <Kim.Robertson@fda.hhs.gov>
Subject: NDA 209115; rucaparib--USPI
Importance: High

Dear Jeri,

Please see the attached MS Word document of Clovis Oncology's USPI for Rubraca™ (rucaparib) for NDA 209115, with DOP1 comments and revisions. We ask that you review and return to us your comments/revisions of the USPI **by COB, Friday, November 4, 2016. We ask that you don't submit your comments/revisions to Sections 12, 8.6, and 8.7 of the USPI or to the Patient Package Insert (PPI) at this time.**

Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

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

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

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(P): 240-402-5364

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/s/

SAKAR M WAHBY
11/01/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Friday, October 28, 2016 11:57 AM
To: 'Jeri Beltman'
Cc: 'Hanna Cho'; Robertson, Kim
Subject: NDA 209115; rucaparib ----Pharmacometric Information Request

Importance: High

Dear Jeri,

In reference to NDA 209115, please see the following information request from the Pharmacometrics team:

Pharmacometrics Information Request:

Reference is made to your report titled “QS-CLV-007: ADDENDUM TO EXPOSURE-RESPONSE REPORT”

Please conduct the following analysis:

- 1. Evaluate the relationship between exposure and maximum % change in the sum of diameters of tumor target lesions (IRR). Doses administered after the assessment time of the maximal change of target lesions should not be included for the calculations of the exposure metrics.**
- 2. Please generate a scatter plot where x axis is sum of target lesion diameters by IRR and y axis is the sum of target lesion diameters by investigator. All ITT subjects who had both IRR and investigator assessment should be included. Each dot represents one radiology screening.**
- 3. Please compare the tumor sizes assessed by investigator and IRR over time. Show boxplots of IRR assessed tumor size vs. investigator assessed tumor size at each visit. All ITT subjects who had both IRR and investigator assessment should be included. Each data point represents one radiology screening.**
- 4. Compare the tumor sizes assessed by investigator and IRR over time at the lower exposure quantile (Q1 and Q2 respectively). Rucaparib exposure metrics definition should be consistent with the one in your addendum of E-R report (AUCss computed based on the average dose from the first dose to the time of the relevant event, e.g., PD, confirmed response). Both exposure metrics based on investigator and IRR assessed ORR should be evaluated.**

Please respond **by 3:00 pm EST., Friday, November 4, 2016.** Submit all relevant datasets and control streams for the above analysis. Refer to the pharmacometrics data submission guideline (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm18048.htm>)

Feel free to contact me if you have any questions and kindly confirm receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

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

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

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/s/

SAKAR M WAHBY
10/28/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, October 27, 2016 2:50 PM
To: Jeri Beltman
Cc: 'Hanna Cho'; Robertson, Kim
Subject: NDA 209115; rucaparib--USPI
Attachments: 10-27-16 FDA revised Rucaparib USPI.docx

Importance: High

Dear Jeri,

Please see the attached MS Word document of Clovis Oncology's USPI for Rubraca™ (rucaparib) for NDA 209115, with DOP1 comments and revisions. We ask that you review and return to us your comments/revisions of the USPI **by COB, Friday, November 4, 2016.** **We ask that you don't submit your comments/revisions to Sections 12, 8.6, and 8.7 of the USPI or to the Patient Package Insert (PPI) at this time.**

Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP1
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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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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SAKAR M WAHBY
10/27/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Thursday, October 27, 2016 3:21 PM
To: 'Jeri Beltman'
Cc: Robertson, Kim; 'Hanna Cho'
Subject: NDA 209115; rucaparib--TCON

Importance: High

Dear Jeri,

In reference to NDA 209115, the Agency would like to have a teleconference with your team to discuss the indication as it relates to the companion diagnostics. We have scheduled a TCON between your firm and the FDA for **Thursday November 3, 2016 at 12:00 pm- 12:30 pm EST.**

Teleconference information:

Audio: Call-in number: (b) (4)
Meeting ID number: (b) (4)

I'm sending this information on behalf of my colleague Kim Robertson while she's on leave this week, Kim might update the TCON call-in information when she returns on Tuesday November 1st. Feel free to contact me if you have any questions and kindly confirm receipt of this email.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
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/s/

SAKAR M WAHBY
10/27/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, October 26, 2016 7:43 AM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Dear Jeri,

FDA is requesting the safety population.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, October 25, 2016 5:41 PM
To: Wahby, Sakar
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Dear Sakar-

Clovis acknowledges the receipt of this information request. Please confirm that FDA is requesting this information for those studies included in the primary efficacy population: CO-338-010 and CO-338-017. Or, is FDA interested in the studies included in the safety population: CO-338-010, CO-338-017, and CO-338-023?

We await conformation of the studies to be included in this response. Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Wahby, Sakar [<mailto:Sakar.Wahby@fda.hhs.gov>]
Sent: Tuesday, October 25, 2016 1:44 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>

Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hi Jeri,

In reference to NDA 209115, please see the following information request from the clinical team:

Clinical Information Request:

- 1. Identify in the submission, or provide electronic versions of, the Pathology Charter for each trial in the submission that documents the chain of custody of patient samples and the de-identification process.**

Please respond **by COB, Thursday, October 27, 2016.** Feel free to contact me if you have any questions and kindly confirm receipt of this email communication.

Thank you,

Sakar

Sakar Wahby, PharmD

Regulatory Project Manager / DOP₁

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

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

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/s/

SAKAR M WAHBY
10/26/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Wednesday, October 26, 2016 7:56 AM
To: 'Jeri Beltman'
Cc: Hanna Cho; Robertson, Kim
Subject: NDA 209115; rucaparib ----Clinical Information Request
Attachments: ir-20161020a-response.pdf

Importance: High

Dear Jeri,

In reference to the Clinical IR dated October 20, 2016, and in reference to your response to this IR dated October 24, 2016 (see email below and attachment), please see the following Clinical IR:

Clinical Information Request:

Please break down the response to this IR for the safety population and the efficacy population. To further clarify: of the patients in the efficacy population, how many sites enrolled patients, and what countries; of the patients in the safety population, how many sites enrolled patients, and what countries?

Please respond **by COB, Thursday, October 27, 2016.** Feel free to contact me if you have any questions and kindly confirm receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
sakar.wahby@fda.hhs.gov
(P): 240-402-5364
(F): 301-796-9845

From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Monday, October 24, 2016 2:40 PM
To: Robertson, Kim; Wahby, Sakar
Cc: Jeri Beltman
Subject: RE: NDA 209115; rucaparib ----Clinical Information Request

Dear Kim and Sakar,

Please find attached as a courtesy copy of Clovis response to the clinical information request shown below. This will be formally submitted to NDA 209,115 via ESG today.

Kind regards,
Hanna

Hanna H. Cho, PhD, RAC
Manager, Regulatory Affairs
Clovis Oncology, Inc. | San Francisco, CA, USA
Office +1.415.409.5491 | Mobile + (b) (6) | hcho@clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, October 20, 2016 11:27 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib ----Clinical Information Request

Hello again Jeri:

Please see the following request for information from my clinical reviewer:

CLINICAL INFORMATION REQUEST:

- For protocol CO-338-017: Page 16 of the study report body mentions 54 sites; however, appendix 16.1.4 contains a list of 50 sites. Provide an explanation for this discrepancy and the actual number of sites, along with the number of sites/country for all non-US sites.

Please provide a response to address this IR by **Monday, October 24, 2016, 3:00pm, EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

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/s/

SAKAR M WAHBY
10/26/2016

Wahby, Sakar

From: Wahby, Sakar
Sent: Tuesday, October 25, 2016 4:44 PM
To: Jeri Beltman
Cc: 'Hanna Cho'
Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hi Jeri,

In reference to NDA 209115, please see the following information request from the clinical team:

Clinical Information Request:

- 1. Identify in the submission, or provide electronic versions of, the Pathology Charter for each trial in the submission that documents the chain of custody of patient samples and the de-identification process.**

Please respond **by COB, Thursday, October 27, 2016.** Feel free to contact me if you have any questions and kindly confirm receipt of this email communication.

Thank you,
Sakar

Sakar Wahby, PharmD
Regulatory Project Manager / DOP₁
Office of Hematology & Oncology Products (OHOP) / CDER/ FDA
10903 New Hampshire Avenue / Bldg 22, Room 2133 / Silver Spring, MD 20993
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/s/

SAKAR M WAHBY
10/25/2016

Robertson, Kim

From: Robertson, Kim
Sent: Friday, October 21, 2016 4:35 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com); Alebachew, Elleni
Subject: NDA 209115; rucaparib----Clinical PMRs & Milestone Dates

Hello Jeri:

Please see below the 2 PMRs from our Clinical Discipline, as they pertain to Clovis' NDA for Rucaparib. The Clinical Discipline is asking for milestone dates for the following:

PMR #1

ARIEL3:

Expected trial completion date:
Expected final report submission date for PFS:
Expected final report submission date for OS:

PMR #2

ARIEL4:

Expected first patient in date:
Expected trial completion date:
Expected final report submission date for PFS:
Expected final report submission date for OS:

Please provide a response to this query by **Monday, October 24, 2016, 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
10/21/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, October 20, 2016 2:27 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib ----Clinical Information Request

Hello again Jeri:

Please see the following request for information from my clinical reviewer:

CLINICAL INFORMATION REQUEST:

- For protocol CO-338-017: Page 16 of the study report body mentions 54 sites; however, appendix 16.1.4 contains a list of 50 sites. Provide an explanation for this discrepancy and the actual number of sites, along with the number of sites/country for all non-US sites.

Please provide a response to address this IR by **Monday, October 24, 2016, 3:00pm, EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
10/20/2016

Robertson, Kim

From: Robertson, Kim
Sent: Monday, October 17, 2016 5:48 PM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib---Clinical Information Request
Attachments: Final MidCycle Communication Agency NME NDA 209115 Rucaparib.doc

Importance: High

Hello Jeri:

Please see the attached Word .doc, as it contains the agenda for the upcoming Mid-Cycle Communication Meeting.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [mailto:jbeltman@clovisoncology.com]
Sent: Monday, October 17, 2016 10:44 AM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Dear Kim-

Clovis accepts the invitation to the MCM teleconference on Thursday October 20th. We will finalize the Clovis attendee list once we have had a chance to review the agenda (expected Tuesday), and reply again with the final sponsor attendee list.

Thanks, Jeri

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, October 13, 2016 1:18 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Hello Jeri:

I will absolutely forward your requests for clarification to the requesting Clinical reviewer and let you know if his response, once I receive feedback from him.

Yes; we are holding the Mid Cycle Communication Meeting (MCM) with Clovis, Inc. on **Thursday, October 20, 2016** between 1:00pm and 2:00pm EST to discuss our findings/any significant review issues up to that date. Please use the following call-in information for the MCM:

Teleconference information

1. Local: (b) (4)
toll free: (b) (4)
2. Follow the instructions that you hear on the phone.
Cisco Unified MeetingPlace meeting ID: (b) (4)

I will provide Clovis with an MCM Agenda by Tuesday, October 18, 2016. I will also provide Clovis with a formal MCM document no later than 30 days following the meeting, because minutes will be taken.

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Thursday, October 13, 2016 2:57 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Dear Kim-

Clovis acknowledges the receipt of this information request. Also, we are seeking clarification on a few points.

Item #1: Clovis believes that the last sentence in Item #1 "Explain the difference in the exposure-response relationships for INV vs IRR, citing specific patient findings that result in the observed differences." refers to the Exposure-Response addendum (QS-CLV-007) submitted as Sequence 007 on August 29th. Please confirm that the reviewers is looking for an explanation regarding the differences between the INV and IRR groups described in that report.

Item #2: Clovis believes that in the first sentence of Item #2 "Indicate in your submission, or justify with reference to available literature, why the objective response rate demonstrated in your trial is better than best available therapy for patients with BRCAm ovarian cancer following two lines of chemotherapy." is a request for an analysis that includes patients who have had precisely 2 prior therapies (as opposed to 2 or more prior therapies). Please confirm that our understanding of the patient group (2 prior therapies) is correct.

In addition, I am seeking to better understand what to expect in the coming weeks. Can we expect to be invited to a teleconference with FDA on October 20th? Or, could the teleconference occur at a later date in order to afford FDA time to review the response to this IR. Should Clovis expect a formal mid-cycle letter prior to the teleconference? Also, assuming that FDA will propose an agenda for the teleconference, when can Clovis expect to see that?

I will try to reach you by phone to follow up on the above. Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, October 12, 2016 12:31 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib---Clinical Information Request
Importance: High

Hello Jeri:

Please see the following request for information from my clinical discipline, as they continue their review of Clovis' NDA for rucaparib:

CLINICAL INFORMATION REQUEST:

- 1) Provide narratives of patient clinical course and clinical response assessment by the investigator for the following 16 patients. Include information about the patients' overall health status, how they tolerated treatment, characteristics of target lesions, timepoint when these patients ultimately progressed/came off study/died and their disposition. Contrast INV findings with IRR findings for these patients and provide some explanation for the discrepancy. Explain the difference in the exposure-response relationships for INV vs IRR, citing specific patient findings that result in the observed differences.

SUBJID	SITEID
042217	04
092218	09
112201	11
14001-206	14001
14001-217	14001
14001-505	14001

14007-506	14007
14008-506	14008
16002-201	16002
16002-202	16002
28001-508	28001
32002-502	32002
32008-203	32008
32018-204	32018
602227	60
802207	80

- 2) Indicate in your submission, or justify with reference to available literature, why the objective response rate demonstrated in your trial is better than best available therapy for patients with BRCAm ovarian cancer following two lines of chemotherapy. Include a description of ORR with best available therapy for platinum-resistant and platinum-refractory ovarian cancer with BRCAm in this line of treatment to justify including that patient population in the indication.

Please provide responses to address these queries by **Tuesday, October 18, 2016, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

PDUFA V Program Mid-Cycle Communication Agenda Template

Meeting Date: Thursday, October 20, 2016
1:00pm-2:00pm, EST
Application Number: NDA 209115
Product: RUBRACA[®] (rucaparib)
Applicant Name: Clovis, Inc.
Proposed Indication: RUBRACA[®] is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy treatment of advanced ovarian cancer in patients with deleterious BRCA-mutated tumors, inclusive of both germline BRCA and somatic BRCA mutations (as detected by an FDA approved test), and who have been treated with two or more chemotherapies.

FDA Attendees:

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Cross Discipline Team Leader, DOP1
Sanjeeve Balasubramaniam, MD, PhD, Clinical Reviewer, DOP1
Sara Horton, MD, Clinical Reviewer, DOP1
Laura Fernandes, PhD, Biometrics Reviewer, OBP
Shenghui Tang, PhD, Biometrics Team Leader, OBP
Jinzhong Liu, PhD, Clinical Pharmacology Reviewer, DPM
Sarah Schrieber, PharmD, Clinical Pharmacology Reviewer, DCP5
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP5
Chao Liu, PharmD, Pharmacometrics Reviewer, DPM
Jingyu (Jerry) Yu, PhD, Pharmacometrics Team Leader, DPM
Haw-Jyh (Brian) Chiu, PhD, Non-Clinical Reviewer, DHOT
Todd Palmby, PhD, Non-Clinical Team Leader, DHOT
Monica Cooper, PhD, Drug Substance Reviewer, OPQ
Xing Wang, PhD, Drug Product Reviewer, OPQ
Xiao Chen, PhD, Acting CMC Team Leader, OPQ
Rosane Charlab-Orbach, PhD, Genomics Team Leader, GTTG
Kim J. Robertson, Regulatory Health Project Manager, DOP1

Applicant Attendees:

TBD

Eastern Research Group Attendees:

(b) (6), Eastern Research Group, Inc.

1. 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. Significant Review Issues

We currently do not have any significant review issues that could preclude the approval of this application.

Please note that our review is ongoing and we will have post-marketing requirements and commitments.

3. Information Requests

Outstanding/New information requests include:

Clinical:

1. Information request sent October 12, 2016, which revolves around discrepancies between Investigator and IRR assessments and exposure-response relationships, and further justification of accelerated approval referencing comparable available treatments.

4. Major Safety Concerns

All major safety concerns can be addressed through review of the submission and the responses to our information requests.

5. Risk Management Update:

At this time, it does not appear a REMS will be required.

6. Advisory Committee Meeting Plans:

An Advisory Committee meeting is not planned.

7. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

This application has been identified for early action under an expedited review. We intend to send you the Late Cycle Meeting (LCM) background package by Tuesday, November 8, 2016. The Late Cycle Meeting is currently scheduled for November 10, 2016; 1:00pm- 2:30pm, Eastern Standard Time. You may choose to change this face-to-face meeting to a teleconference, or cancel the meeting altogether if you feel it is not needed given our continued and regular communications.

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/s/

KIM J ROBERTSON
10/18/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, October 18, 2016 12:20 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hi Jeri:

Please see the following clinical request for information, relative to Clovis' rucaparib NDA:

CLINICAL INFORMATION REQUEST:

1. Identify the location in the submission or provide further details regarding the specific type of arrhythmia that was experienced by patient 16005-202 in study CO-338-017 (i.e. Vtach, bradycardia, afib).
2. Identify the location in the submission or provide an additional summary table of TEAEs by age for the following groups of patients (as columns) patients <65 years, ≥65 to <75 years, ≥75 years, and ≥65 yrs, in the ovarian cancer safety population (N=378), by the following rows:
 - Patients with one of more TEAE
 - Patient with one or more Serious TEAE
 - Patients with one or more TEAE of grade 3 or higher
 - Patient with one or more TEAE leading to death
 - Patients with one or more TEAE leading to dose reduction
 - Patients with one or more TEAE leading to dose interruption
 - Patients with TEAE leading to discontinuation

Please provide responses to address these queries by **Monday, October 24, 2016, 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845*

Email: kim.robertson@fda.hhs.gov

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/s/

KIM J ROBERTSON
10/18/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, October 18, 2016 4:28 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib--Clinical Pharmacology Request for Information

Importance: High

Hi again Jeri:

Please see below the request for information from our clinical pharmacology reviewer:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

Reference is made to your reports titled "QS-CLV-006: POPULATION PHARMACOKINETICS REPORT" and "QS-CLV-007: ADDENDUM TO EXPOSURE-RESPONSE REPORT"

1. In the PPK analysis, the concomitant drugs were treated as a time independent covariates. The timing of the co-administration of other drugs should be considered in the analysis. Please clarify if the timing of administration of concomitant drugs was available, if so, please evaluate the effect of concomitant drugs on rucaparib PK by treating them as time-varying covariates in PPK analysis **and submit the report no later than October 25, 2016, 3:00pm EST.**
2. In the "Addendum to Exposure-Response Analysis", doses administered after the time of confirmed response or progressive diseases were not included for the calculations of the exposure for both investigator and IRR response. Please provide the time to the last dose used to generate these exposure metrics for each subject (both investigator and IRR assessed ORR) no later than **October 21, 2016, 3:00pm EST.**

Submit all relevant datasets and control streams for the above analysis. Refer to the pharmacometric data submission guideline

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm18048.htm>) for more information.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

*Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
10/18/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

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

Drug Process:

(b) (4)

(b) (4)

5. You have stated that section 3.2.P of your application would be updated in response to previous process related information requests, but you have not updated section 3.2.P. Please update section 3.2.P to agree with your responses provided on 09/23/2016 and your responses to this information request.

(b) (4)

Biopharmaceutics:

7. The proposed dissolution acceptance criterion of “Q = (b) (4)” is not acceptable, and the dissolution data provided support a tighter acceptance criterion of “Q = (b) (4) at 15 min”. Implement the recommended dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

Drug Substance and Drug Product:

8. Submit the full report for the forced degradation study described in your responses to IR-20160830a (item #2) and IR-20160906a (item #1), including raw chromatograms, tabular analytical results and peak purity plots, etc.

Please respond to these comments by COB October 24, 2016.

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,
Kristine F. Leahy
-S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2016.10.11 16:59:23 -04'00'

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



Xiao
Chen

Digitally signed by Xiao Chen

Date: 10/11/2016 10:44:12PM

GUID: 508da7220002a138fcc70fbccbfd08bf

Robertson, Kim

From: Robertson, Kim
Sent: Friday, October 07, 2016 3:27 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib----DMEPA Carton and Container Comment

Hello again Jeri:

As our review for Clovis' rucaparib NDA remains underway, our DMEPA Reviewer has ascertained the following comment, relative to the container labels:

DMEPA CONTAINER COMMENT:

- Remove the word (b) (4) from the strength statement "#00 mg* (b) (4) to reduce information crowding on the principal display panel.

Please provide updated container information no later than **Monday, October 17, 2016**.

-Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
10/07/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, September 29, 2016 10:39 AM
To: 'Hanna Cho'
Cc: Jeri Beltman
Subject: RE: NDA 209115; rucaparib----Additional Clinical Information Request

Hi Hanna:

As I anticipated, a response by Friday is fine with the reviewer. The reviewer has an additional request to add-on to the IR that we'd like to have a response to by Friday as well:

- On page 8 in your response to IR-20160818a (NDA209115) regarding hepatic impairment, please clarify the number of patients with mild and moderate hepatic impairment.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Wednesday, September 28, 2016 3:52 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115; rucaparib----Additional Clinical Information Request

Many thanks, Kim!

Hanna H. Cho, PhD, RAC
Manager, Regulatory Affairs
Clovis Oncology, Inc. | San Francisco, CA, USA
Office +1.415.409.5491 | Mobile (b) (6) | hcho@clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, September 28, 2016 1:50 PM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: RE: NDA 209115; rucaparib----Additional Clinical Information Request

Let me check with my clinpharm folks Hanna. If Friday is the earliest day you can provide the information, I'm sure that will be fine.

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Wednesday, September 28, 2016 2:46 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115; rucaparib----Additional Clinical Information Request
Importance: High

Dear Kim,

Clovis confirms the receipt of this information request. Clovis is currently working to gather information needed, but it is projected to be in need one more day to put the response together. Clovis would like to propose the due date of Friday September 30 2016 for the response to this information request.

Please kindly confirm the receipt of this email and the updated due date proposal is acceptable.

Kind regards,
Hanna

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, September 28, 2016 9:51 AM
To: Hanna Cho <hcho@clovisoncology.com>
Cc: Jeri Beltman <jbeltman@clovisoncology.com>
Subject: NDA 209115; rucaparib----Additional Clinical Information Request
Importance: High

Hello again Hanna:

Please see the additional request for information from my clinical pharmacology team:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

- Please refer to the page 8 of 21 in your response to IR-20160818a under NDA209115 regarding pooled data for mild and moderate renal impairment. Please re-analyze your data for patients with separated groups of mild and moderate renal impairment.

Please submit these results also by **Thursday, September 29, 2016; 12:00PM, EDT.**

-K

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

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/s/

KIM J ROBERTSON
09/29/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, September 29, 2016 1:31 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Hi Jeri:

Please see the following request for information from our clinical reviewers, relative to the rucaparib NDA:

CLINICAL INFORMATION REQUEST:

- Please clarify if patients with MDS/Leukemia on Study CO-338-014 had their study treatment unblinded for the purpose of this NDA. In the summary of clinical safety, it appears we do not know the treatment arm of these patients; however, in table 2.7.4-23 in the outcome column, it states “discontinued rucaparib treatment”. Were these two patients on the rucaparib arm? Or is that just being assumed?

Please provide a response to address this query by **Friday, September 30, 2016, 3:00pm EDT**.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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KIM J ROBERTSON
09/29/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 28, 2016 10:35 AM
To: 'Hanna Cho'
Cc: Jeri Beltman
Subject: RE: NDA 209115--Response to Clovis' re: Clinical Pharmacology IR

Hello Hanna:

Reference is made to your "Response to FDA Request for Clinical Pharmacology Information (20160909a) dated September 22nd "

- Please submit the relevant code and datasets for the time to event analysis (time to first dose modification or reduction). Datasets and codes should be submitted with define files.

Please provide a response to address this information request no later than **Thursday, September 29, 2016, 12:00PM EDT.**

-Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Hanna Cho [<mailto:hcho@clovisoncology.com>]
Sent: Thursday, September 22, 2016 1:23 PM
To: Robertson, Kim
Cc: Jeri Beltman
Subject: RE: NDA 209115--Response to Clovis' re: Clinical Pharmacology IR

Dear Kim,

Please find attached as Clovis responses to this clinical pharmacology information request. It is also formally submitted to NDA 209,115 via ESG today.

Kind regards,
Hanna

Hanna H. Cho, PhD, RAC
Manager, Regulatory Affairs
Clovis Oncology, Inc. | San Francisco, CA, USA

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, September 09, 2016 11:11 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115--Response to Clovis' re: Clinical Pharmacology IR

Hello again Jeri:

Pertinent to Clovis' August 29th response to our clinical pharmacology IR:

Dear Kim-

This message is to let you know that the responses to two separate information requests were submitted to NDA 209,115 today. A courtesy copy is attached for your reference. These clinical pharmacology responses are more extensive than some of the past ones. Therefore, Clovis wishes to confirm that this answers the reviewer's questions, and if not suggest that we might schedule a teleconference to work through any remaining details. Confirmation from the reviewer that we have satisfied the request would be appreciated.

The CP reviewer has stated the following:

Your responses to our request for information are acceptable in general. However, for the figures (Figure 1 and Figure 2) in your response to IR-20160816a, the Kaplan-Meier plot (time to event analysis) should be provided by including all patients for ER for safety analysis. Patients without dose interruption/reduction should be treated as censored subjects at the time of the end of treatment.

Please submit the results and relevant datasets/program by **Thursday, September 22, 2016, 3:00pm EDT**.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

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KIM J ROBERTSON
09/28/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 28, 2016 11:51 AM
To: Hanna Cho (hcho@clovisoncology.com)
Cc: jbeltman@clovisoncology.com
Subject: NDA 209115; rucaparib----Additional Clinical Information Request

Importance: High

Hello again Hanna:

Please see the additional request for information from my clinical pharmacology team:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

- Please refer to the page 8 of 21 in your response to IR-20160818a under NDA209115 regarding pooled data for mild and moderate renal impairment. Please re-analyze your data for patients with separated groups of mild and moderate renal impairment.

Please submit these results also by **Thursday, September 29, 2016; 12:00PM, EDT.**

-K

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/28/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, September 20, 2016 5:18 PM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib----Clinical Information Request

You are most welcome Jeri.

-K

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [mailto:jbeltman@clovisoncology.com]
Sent: Tuesday, September 20, 2016 5:15 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib----Clinical Information Request

Thanks very much for providing this clarification. Jeri

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Tuesday, September 20, 2016 2:12 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: RE: NDA 209115; rucaparib----Clinical Information Request

Hi Jeri:

Regarding item #2, the reviewer is asking that we start with the patients in the **efficacy** population.

-K

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845*

Email: kim.robertson@fda.hhs.gov

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, September 19, 2016 5:10 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib----Clinical Information Request

Dear Kim-

Clovis acknowledges the receipt of this information request. We are seeking a clarification with regard to item #2. Please confirm that the patients to be include for item #2 are the ARIEL2 patients who are included in the efficacy population. Or, is FDA asking about all ARIEL2 patients included in the safety population?

Thanks in advance for the clarification, as we aim to provide the information required.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, September 16, 2016 2:22 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib----Clinical Information Request

Hello Jeri:

Please see the following request for information, as it pertains to Clovis' rucaparib NDA:

CLINICAL REQUEST FOR INFORMATION:

1. Provide a table by patient ID (efficacy population only - 106 rows), with columns as follows:

- What test result enrolled the patient on the trial (local germline blood, tissue FM, etc.)
- BRCA germline local testing result
- CTA result,
- CDx result,
- conclusion column specifying germline or somatic)

2. (more details for the same question as above)

For Study CO-338-017, provide a description of the genetic testing hierarchy used for patient treatment eligibility for the various parts of the study and consistent with the amendments. For example, some patients in part 1 were required to have gBRCA status known for eligibility, and some of these patients later had the CTA test and/or the CDx test, potentially guided by protocol amendments. Other patients in the study apparently didn't have gBRCA testing prior to protocol treatment. Enumerate the various pre-treatment BRCA determination pathways and identify which patients were tested using that pathway, specifying the test used for protocol treatment eligibility. Also identify patients who had BRCA testing after treatment, and whether the testing was in blood/buccal, tumor tissue, or both.

For example:

Method 1: Genomic testing◊Enrollment and treatment◊tumor tissue CTA testing◊tumor tissue CDx testing: Pts a, b, c, etc.

Method 2: Genomic testing◊Enrollment and treatment

Method 3: Tumor tissue CTA testing◊Enrollment and treatment

Method 4: Tumor tissue CTA testing◊Tumor tissue CDx testing◊Enrollment and treatment◊genomic testing

Method 5: Tumor tissue CTA testing◊Enrollment and treatment◊Tumor tissue CDx testing◊genomic testing

Method 6: Tumor tissue CTA testing◊Tumor tissue CDx testing◊Enrollment and treatment
Etc.

3) Please also provide a dataset of patients for whom additional testing results are pending/will be provided for this NDA, and what type of testing.

Please provide responses to address these queries by **Friday, September 23, 2016, 4:00pm EDT.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/20/2016

From: Robertson, Kim
Sent: Friday, September 16, 2016 5:22 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib----Clinical Information Request

Hello Jeri:

Please see the following request for information, as it pertains to Clovis' rucaparib NDA:

CLINICAL REQUEST FOR INFORMATION:

1. Provide a table by patient ID (efficacy population only - 106 rows), with columns as follows:

- What test result enrolled the patient on the trial (local germline blood, tissue FM, etc.)
- BRCA germline local testing result
- CTA result,
- CDx result,
- conclusion column specifying germline or somatic)

2. (more details for the same question as above)

For Study CO-338-017, provide a description of the genetic testing hierarchy used for patient treatment eligibility for the various parts of the study and consistent with the amendments. For example, some patients in part 1 were required to have gBRCA status known for eligibility, and some of these patients later had the CTA test and/or the CDx test, potentially guided by protocol amendments. Other patients in the study apparently didn't have gBRCA testing prior to protocol treatment. Enumerate the various pre-treatment BRCA determination pathways and identify which patients were tested using that pathway, specifying the test used for protocol treatment eligibility. Also identify patients who had BRCA testing after treatment, and whether the testing was in blood/buccal, tumor tissue, or both.

For example:

Method 1: Genomic testing → Enrollment and treatment → tumor tissue CTA testing → tumor tissue CDx testing: Pts a, b, c, etc.

Method 2: Genomic testing → Enrollment and treatment

Method 3: Tumor tissue CTA testing → Enrollment and treatment

Method 4: Tumor tissue CTA testing → Tumor tissue CDx testing → Enrollment and treatment → genomic testing

Method 5: Tumor tissue CTA testing↗Enrollment and treatment↗Tumor tissue CDx testing↗genomic testing

Method 6: Tumor tissue CTA testing↗Tumor tissue CDx testing↗Enrollment and treatment
Etc.

3) Please also provide a dataset of patients for whom additional testing results are pending/will be provided for this NDA, and what type of testing.

Please provide responses to address these queries by **Friday, September 23, 2016, 4:00pm EDT.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/16/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 14, 2016 11:08 AM
To: 'Jeri Beltman'
Cc: 'Hanna Cho'
Subject: RE: NDA 209115; rucaparib----Clinical Request for Information

Jeri, after checking with requesting reviewer, I was asked to notify you/Clovis to hold off on responding to this particular request.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Robertson, Kim
Sent: Wednesday, September 14, 2016 9:18 AM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib----Clinical Request for Information

Hello Jeri:

Apologies; I should've responded to you by letting you know the requesting clinical reviewer informed me that he was going to look further into this matter to see if his IR will remain relevant. As soon as he finishes investigating something on his end, he will notify me and I will in turn update you.

Thank you for your patience.

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Monday, September 12, 2016 2:53 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib----Clinical Request for Information

Dear Kim-

Clovis acknowledges this request. However, it is not clear to us what FDA is asking for. The patients listed below are included in the primary efficacy population (N=106). If there is a specific attribute or a specific place in the NDA you are asking about then please provide that additional information. Pending further information, all we can do is confirm that these patients are part of the primary efficacy population.

We will await further clarification before preparing an official response.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, September 12, 2016 11:15 AM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib----Clinical Request for Information

Hello Jeri:

Please see the following request for information from our clinical discipline:

CLINICAL INFORMATION REQUEST:

Please describe why the following patients from Study 17 were not included in the efficacy population:

CO-338-017-32021-201

CO-338-017-14001-504

CO-338-017-14004-501

CO-338-017-28001-502

CO-338-017-28001-504

CO-338-017-32003-503

Please provide us with a response to address this query by **Wednesday, September 14, 2016, 12Noon EDT.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/14/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 14, 2016 11:40 AM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: RE: NDA 209115; rucaparib---Clinical Information Request

Apologies Jeri:

I just noticed a typo in the first sentence of my previous e-mail requesting information..... the NDA should read "209115" as opposed to "NDA 209915".

-Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Robertson, Kim
Sent: Wednesday, September 14, 2016 11:36 AM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Hello again Jeri:

I do have a new information request from our clinical reviewer for NDA (b) (4) rucaparib and it is as follows:

CLINICAL INFORMATION REQUEST:

- Per the documents submitted on August 4, 2016, five deaths had occurred on study. Submit narratives for each patient, who has experienced a death on study to date.

Please provide responses to address this query by **Wednesday, September 28, 2016, 3:00 EDT.**

Regards,

Kim

Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

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/s/

KIM J ROBERTSON
09/14/2016

Robertson, Kim

From: Robertson, Kim
Sent: Friday, September 09, 2016 2:10 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115--Response to Clovis' re: Clinical Pharmacology IR

Hello again Jeri:

Pertinent to Clovis' August 29th response to our clinical pharmacology IR:

Dear Kim-

This message is to let you know that the responses to two separate information requests were submitted to NDA 209,115 today. A courtesy copy is attached for your reference. These clinical pharmacology responses are more extensive than some of the past ones. Therefore, Clovis wishes to confirm that this answers the reviewer's questions, and if not suggest that we might schedule a teleconference to work through any remaining details. Confirmation from the reviewer that we have satisfied the request would be appreciated.

The CP reviewer has stated the following:

Your responses to our request for information are acceptable in general. However, for the figures (Figure 1 and Figure 2) in your response to IR-20160816a, the Kaplan-Meier plot (time to event analysis) should be provided by including all patients for ER for safety analysis. Patients without dose interruption/reduction should be treated as censored subjects at the time of the end of treatment.

Please submit the results and relevant datasets/program by **Thursday, September 22, 2016, 3:00pm EDT**.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/09/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, September 06, 2016 3:18 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Hello Jeri:

Please see the following clinical request for information, as our review for NDA 209115; rucaparib remains underway:

CLINICAL REQUEST FOR INFORMATION:

- Provide, or identify in the submission the case report forms for patients 012209 and 013303 from Study 10.

Please provide a response to this request by **Wednesday, September 7, 2016, 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/08/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 07, 2016 5:04 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hello again ladies:

Please see the following clinical request for information, as our review for NDA 209115; rucaparib remains underway:

CLINICAL REQUEST FOR INFORMATION:

- Identify in the submission, or provide, the SDTM dataset for study co-338-017 for concomitant medications (CM).

Please provide a response to this request by **Thursday, September 8, 2016, 3:00pm EST**.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
09/08/2016



NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

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

Drug Product:

- 1) Repeat forced degradation studies of Rucaparib drug product using in-house (b) (4) (b) (4) for Analysis of Degradation Products in Rucaparib drug product to demonstrate the method is stability indicating and can capture all the potential degradation products if present. (b) (4)
- 2) Evaluate intermediate precision of the (b) (4) for Analysis of Degradation Products (b) (4).
- 3) Since there is no specified degradation impurity in the Rucaparib drug product specifications, we recommend that you use one of drug product forced degradation study samples, (b) (4)

Please respond to Drug Product comments by COB September 16, 2016.

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,

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

*Entered Sept. 6, 2016
in Panorama*



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

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

Drug Process:

- 1) We acknowledge that you are proposing a (b) (4) kg commercial batch size for your final blend. Discuss the commercial batch sizes for (b) (4) of both dosage strengths.
- 2) (b) (4)
- 3) A (b) (4) statement was not located in section 3.2.P.3.3 of your submission. Please provide a (b) (4) statement for your drug product manufacturing.
- 4) (b) (4)

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

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

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

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200181597
7, cn=Kristine F. Leahy -S
Date: 2016.08.30 14:21:47 -04'00'

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



Kristine
Leahy

Digitally signed by Kristine Leahy
Date: 8/30/2016 02:28:10PM
GUID: 55f72bd9003d99948f388d681cbec17d



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

We also refer to your July 22, 2016 submission, containing Quality Response to Information Request regarding the drug substance forced degradation study in Section 3.2.S.4.3.

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

Drug Substance:

(b) (4)

2. In your response (dated July 22, 2016) to the CMC deficiency regarding the drug substance forced degradation study in Section 3.2.S.4.3, you referenced the drug product forced degradation study. (b) (4)
(b) (4) develop a better method for monitoring drug degradation products in the drug substance (b) (4)
(b) (4) Provide a copy of the new or revised analytical procedure and the validation report.

Please respond to Drug Substance comments by COB September 12, 2016.

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,

Kristine F. Leahy

-S

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

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2016.08.30 11:53:58 -04'00'



NDA 209115

PRIORITY REVIEW DESIGNATION

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, received June 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for rucaparib, 200 mg and 300 mg tablets.

We also refer to your submissions dated April 12, 2016 and May 16, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is February 23, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 9, 2016.

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

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
08/22/2016

Robertson, Kim

From: Robertson, Kim
Sent: Friday, August 19, 2016 4:47 PM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Thank you for this Jeri. I will forward the responses on to the requesting reviewer. Relative to your request for clarification for items #3 and #4, I have the following:

- Our request for #3 and #4 is to assess the relationship between the time to the first dose reduction/modification and exposure calculated up until the time of event (i.e., first dose reduction/modification).

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Friday, August 19, 2016 3:38 PM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Dear Kim-

Please find attached the Clovis response to items 1 and 2. A response to items 3 and 4 will be supplied at a later time. Please note that the attached response was also submitted to NDA 209,115.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, August 16, 2016 12:47 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib--Clinical Pharmacology Information Request
Importance: High

Hello Jeri:

Reference is made to Clovis Oncology's August 10, 2016 response to our previous IR:

ADDITIONAL CLINICAL PHARMACOLOGY REQUEST FOR INFORMATION:

Exposure response report (QS-CLV-007 Final Report):

1. Please address the discrepancy between the date of last exposure to treatment in dm.xpt and the last dosing record in ex.xpt. For example, regarding subject CO-338-010-042242, the last exposure was on 6/25/2015 (RFXENDTC) according to dm.xpt. Though the date of the last exposure record for this subject was 6/8/2015 (EXENDTC) in ex.xpt. It suggests that for some patients the dosing records might be incomplete. The dataset is referred as follows:

Study Report for CO-338-010, Tabulation Data:

- dm.xpt (Demographics)
- ex.xpt (Exposure)

Study Report for CO-338-017, Tabulation Data:

- dm.xpt (Demographics)
- ex.xpt (Exposure)

Population PK analysis (QS-CLV-006)

- nmruc-stud1014-10-17-15apr16-csv.xpt
2. If the dosing record in ex.xpt and nmruc-stud1014-10-17-15apr16-csv.xpt is incomplete, please update the ex.xpt as well as nmruc-stud1014-10-17-15apr16-csv.xpt by providing the full dosing record. All 121 subjects in the exposure-efficacy analysis should be included in the updated datasets.
 3. Assess the relationship between drug exposure and time to first dose reduction. In the analysis, exposures after the time of first dose reduction should not be included when exposure metrics are generated.
 4. Assess the relationship between drug exposure and time to first dose modification (including dose reduction/interruption/withdrawl). In the analysis, exposures after

the time of first dose modification should not be included when exposure metrics are generated.

Please provide responses to address items **#1 and #2 by Friday, August 19, 2016; 3:30pm EST.** For the remaining items (#3 and #4), please provide responses to address those by **Monday, August 29, 2016; 3:30pm EST.**

****FYI**.....as a side note---Jeri, please make certain that when Clovis responds to our discipline IRs that the response headings on Clovis' cover letters correlate to our discipline(s) that requested the actual response. Ex.---when Clovis responded to our August 3rd Clinical Pharmacology IR, Clovis' letterhead on the return response stated it was a response to a "Clinical" IR; thereby causing our document room personnel to code and bring the responses/submission to the attention of the clinical reviewers vs. the clinical pharmacology reviewers. A distinction is made in our databases; therefore, we want to continue to ensure that the appropriate disciplines receive the appropriate information in a timely manner.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
08/19/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, August 18, 2016 11:29 AM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Pharmacology Information Request

Importance: High

Hello Jeri:

Please see below the request for information from our Clinical Pharmacology reviewers of Clovis' NDA for rucaparib:

CLINICAL PHARMACOLOGY INFORMATION REQUEST:

For each item, include the results with the appropriate datasets, and where appropriate, provide the program codes used:

1. Dose Proportionality: Evaluate the dose proportionality of rucaparib in terms of $C_{\max}$ and AUC_{0-12hr} using a power model (Reference: Brian Smith et al. Pharmaceutical Research, Vol. 17, No. 10, 2000). In Table 2.7.2-9 of the Summary of Clinical Pharmacology Studies in Module 2.7.2, AUC_{0-12hr} on Days 1 and 15 are missing in some subjects at the dose levels of 240, 360, 480, 600 and 840 mg BID. Consider calculating AUC_{0-12hr} by imputing the concentrations at 12 hours post-dose, please include rationale behind the imputation method.
2. Time-dependence of PK: Evaluate the time-dependence of rucaparib PK (i.e., whether the CL/F changes over time). Provide the following items in your response:
 - a. A plot of the observed steady-state trough concentrations of rucaparib versus time (or treatment cycles) by pooling data from Studies CO-338-010 and CO-338-017
 - b. A plot of the observed CL/F of rucaparib versus time (or treatment cycles) by pooling data from Studies CO-338-010 and CO-338-017
 - c. Testing whether AUC_{0-inf} of single-dose rucaparib is equal to AUC_{0-12hr} of rucaparib at steady state

3. Organ Dysfunction: Evaluate whether dose adjustment may be warranted in patients with hepatic or renal impairment. Provide a summary of the efficacy profile (ORR by Independent Radiologist Review, ORR by Investigator Response Assessment, and Duration of Response), safety profile (Grade 3+ TEAEs and Grade 3+ treatment-related TEAEs) and dose modification records (discontinuation, dose reduction, and dose interruption) in patients with various degrees of hepatic or renal impairment (moderate, mild) in comparison to those in patients with normal hepatic or renal function.

For classification of renal and hepatic function, please refer to the FDA draft Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> and “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

4. Dose Selection: Provide the following in your response:
 - a. For Study CO-338-010 Part 1, provide a summary of efficacy profile (for all treated patients with different cancers), safety profile (Grade 3+ TEAEs and Grade 3+ treatment-related TEAEs), dose modification records (discontinuation, dose reduction, and dose interruption) and demographics in patients at different dose levels of 240, 360, 480, 600 and 840 mg BID
 - b. We note that the clinical dose selection was discussed by you at your presentation to the FDA on July 29, 2016. We request that you please provide a comprehensive written rationale for how the clinical dose of 600 mg BID rather than a lower dose was ultimately selected for evaluation in ovarian cancer

Please provide responses to address these queries by **Friday, September 9, 2016; 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441*

Fax: (301) 796-9845

Email: kim.robertson@fda.hhs.gov

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/s/

KIM J ROBERTSON
08/18/2016

From: Robertson, Kim
Sent: Tuesday, August 16, 2016 3:47 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Importance: High

Hello Jeri:

Reference is made to Clovis Oncology's August 10, 2016 response to our previous IR:

ADDITIONAL CLINICAL PHARMACOLOGY REQUEST FOR INFORMATION:

Exposure response report (QS-CLV-007 Final Report):

1. Please address the discrepancy between the date of last exposure to treatment in dm.xpt and the last dosing record in ex.xpt. For example, regarding subject CO-338-010-042242, the last exposure was on 6/25/2015 (RFXENDTC) according to dm.xpt. Though the date of the last exposure record for this subject was 6/8/2015 (EXENDTC) in ex.xpt. It suggests that for some patients the dosing records might be incomplete. The dataset is referred as follows:

Study Report for CO-338-010, Tabulation Data:

- dm.xpt (Demographics)
- ex.xpt (Exposure)

Study Report for CO-338-017, Tabulation Data:

- dm.xpt (Demographics)
- ex.xpt (Exposure)

Population PK analysis (QS-CLV-006)

- nmruc-stud1014-10-17-15apr16-csv.xpt

2. If the dosing record in ex.xpt and nmruc-stud1014-10-17-15apr16-csv.xpt is incomplete, please update the ex.xpt as well as nmruc-stud1014-10-17-15apr16-csv.xpt by providing the full dosing record. All 121 subjects in the exposure-efficacy analysis should be included in the updated datasets.
3. Assess the relationship between drug exposure and time to first dose reduction. In the analysis, exposures after the time of first dose reduction should not be included when exposure metrics are generated.

4. Assess the relationship between drug exposure and time to first dose modification (including dose reduction/interruption/withdrawal). In the analysis, exposures after the time of first dose modification should not be included when exposure metrics are generated.

Please provide responses to address items **#1 and #2 by Friday, August 19, 2016; 3:30pm EST.** For the remaining items (#3 and #4), please provide responses to address those by **Monday, August 29, 2016; 3:30pm EST.**

****FYI**.....as a side note---Jeri, please make certain that when Clovis responds to our discipline IRs that the response headings on Clovis' cover letters correlate to our discipline(s) that requested the actual response. Ex.---when Clovis responded to our August 3rd Clinical Pharmacology IR, Clovis' letterhead on the return response stated it was a response to a "Clinical" IR; thereby causing our document room personnel to code and bring the responses/submission to the attention of the clinical reviewers vs. the clinical pharmacology reviewers. A distinction is made in our databases; therefore, we want to continue to ensure that the appropriate disciplines receive the appropriate information in a timely manner.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
08/16/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, August 11, 2016 3:01 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: New NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hello Jeri:

Please see the following request for information from my clinical reviewers of the rucaparib NDA:

CLINICAL INFORMATION REQUEST:

- Please identify the location in the submission, or provide a table by patient ID, of all deaths in the total safety analysis population (n=409), ovarian cancer population (n=378), and BRCA population (n=144) by causes of death and timing of death (broken down by treatment period, within 28 days, and in follow up (and if in follow up how long from treatment)).

Please provide a response to address this inquiry by Monday, August 15, 2016; 3:00pm EST.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
08/11/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, August 04, 2016 11:35 AM
To: 'Jeri Beltman'
Cc: 'Hanna Cho'
Subject: RE: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Hello Jeri:

The clinical pharmacology reviewer has confirmed that the scope is limited in the primary efficacy population.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Robertson, Kim
Sent: Thursday, August 04, 2016 11:06 AM
To: 'Jeri Beltman'
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Hi Jeri:

I will submit your request for clarification to my clinpharm reviewer and provide you with a response as soon as I receive feedback from him.

Thank you,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Thursday, August 04, 2016 12:34 AM
To: Robertson, Kim
Cc: Hanna Cho
Subject: RE: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Dear Kim-

This e-mail confirms the Clovis receipt of this information request.

With regard to Question #2, please confirm that this question is limited to the patients in the primary efficacy population (N=106 BRCA^{mut} ovarian cancer patents). If this question relates to a different patient group, then please clarify which patients should be included in the response to Question #2.

With regard to Question #1, I will be meeting with my PK team tomorrow. I will let you know if we have questions or require clarifications on that part of the request after that.

Thanks, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, August 03, 2016 3:04 PM
To: Jeri Beltman <jbeltman@clovisoncology.com>
Cc: Hanna Cho <hcho@clovisoncology.com>
Subject: NDA 209115; rucaparib--Clinical Pharmacology Information Request
Importance: High

Hello again Jeri:

The clinical pharmacology reviewer has the following request for information, as it pertains to Clovis' NDA for rucaparib:

CLINICAL PHARMACOLOGY REQUESTS FOR INFORMATION:

1. Reference is made to your report "Exposure-response relationships for rucaparib in patients with ovarian cancer (QS-CLV-007)"; exposure metrics used in your ER analysis were derived based on dosing record till the end of the treatment. This may lead to bias for ER analysis due to the high rate dose reduction. Please conduct ER analysis using the following approach and submit updated report with all relevant datasets and code.
 - Re-evaluate the relationship between exposure and objective response rate. For confirmed ORR, both investigator and IRC assessed ORR should be analyzed. Doses

administered after the time of confirmed response or progressive disease should not be included for the calculations of the exposure metrics.

- Re-evaluate the relationship between exposure and maximum % change in the sum of diameters of tumor target lesions. Doses administered after the assessment time of the maximal change of target lesions should not be included for the calculations of the exposure metrics.
- Evaluates the relationship between exposure and maximum % change in the serum CA-125. Doses administered after the assessment time of the maximal change of CA-125 should not be included for the calculations of the exposure metrics.

For these inquiries/comments, please provide responses by **Monday, August 29, 2016, 3:00pm EST.**

2. Summarize the causes of progressive disease (i.e., target lesion/non-target lesion/new lesions) according to the RECIST criteria in trial CO-338-010 and CO-338-017. Both investigator and IRC assessed ORR should be assessed.

For this inquiry, please submit a response by **Friday, August 12, 2016, 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
08/04/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, August 03, 2016 6:04 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib--Clinical Pharmacology Information Request

Importance: High

Hello again Jeri:

The clinical pharmacology reviewer has the following request for information, as it pertains to Clovis' NDA for rucaparib:

CLINICAL PHARMACOLOGY REQUESTS FOR INFORMATION:

1. Reference is made to your report "Exposure-response relationships for rucaparib in patients with ovarian cancer (QS-CLV-007)"; exposure metrics used in your ER analysis were derived based on dosing record till the end of the treatment. This may lead to bias for ER analysis due to the high rate dose reduction. Please conduct ER analysis using the following approach and submit updated report with all relevant datasets and code.
 - Re-evaluate the relationship between exposure and objective response rate. For confirmed ORR, both investigator and IRC assessed ORR should be analyzed. Doses administered after the time of confirmed response or progressive disease should not be included for the calculations of the exposure metrics.
 - Re-evaluate the relationship between exposure and maximum % change in the sum of diameters of tumor target lesions. Doses administered after the assessment time of the maximal change of target lesions should not be included for the calculations of the exposure metrics.
 - Evaluates the relationship between exposure and maximum % change in the serum CA-125. Doses administered after the assessment time of the maximal change of CA-125 should not be included for the calculations of the exposure metrics.

For these inquiries/comments, please provide responses by **Monday, August 29, 2016, 3:00pm EST.**

2. Summarize the causes of progressive disease (i.e., target lesion/non-target lesion/new lesions) according to the RECIST criteria in trial CO-338-010 and CO-338-017. Both investigator and IRC assessed ORR should be assessed.

For this inquiry, please submit a response by **Friday, August 12, 2016, 3:00pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
08/03/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 209115

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Clovis Oncology, Inc
5500 Flatiron Parkway
Suite 100
Boulder, CO 80301

ATTENTION: Jeri Beltman, PhD
Senior Director, Regulatory Affairs

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated and received June 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200 mg and 300 mg.

We also refer to your correspondence, dated and received June 23, 2016, requesting review of your proposed proprietary name, Rubraca.

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

If any of the proposed product characteristics as stated in your June 23, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager in the Office of New Drugs at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

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

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/02/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, July 28, 2016 3:39 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib--QT-IRT Information Request

Importance: High

Hello Jeri:

Relative to Clovis' New NDA for rucaparib, our colleagues from the Division of Cardio Renal Products have the following request for information:

QT-IRT INFORMATION REQUEST:

- The ECGs in the ECG Warehouse for Study CO-338-010 do not match those in the clinical dataset (adeg.xpt). Please submit all available ECGs and their corresponding clinical datasets. Please explain why only half of the ECGs are submitted.

Please provide a response by **COB Thursday, August 4, 2016.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
07/28/2016

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, July 28, 2016 4:37 PM
To: jbeltman@clovisoncology.com
Cc: Hanna Cho (hcho@clovisoncology.com)
Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hello again Jeri:

Please see the following clinical request for information re: NDA 209115; rucaparib:

CLINICAL INFORMATION REQUEST:

- The ADAM datasets that identify the BRCA mutant patients included in the efficacy population has 9 patients for whom the mutation status is labeled as “indetermined”. Identify in the submission where this is defined in greater detail.

Please provide a response to this IR by **Friday, July 29, 2016; 12:30pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
07/28/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

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

Drug Product:

1. Provide detailed analytical method validation reports in section 3.2.S.4.3 and section 3.2.P.5.3.
2. Provide method validation package in section 3.2.R.

Please respond to Drug Product comments by COB July 22, 2016.

Drug Substance:

1. In Section 3.2.S.4.3, you provided a validation summary of the Assay and Related Substances by (b) (4) method. The forced degradation study to determine specificity is not sufficient, as you did not meet the target level of (b) (4)% degradation for each stress condition and you did not provide mass balance data. Repeat the study to ensure that the target (b) (4)% degradation (and not more than (b) (4)% degradation) is achieved for each stress condition. Provide the numerical results for assay and impurities, showing mass balance for each stress condition.

Please respond to Drug Substance comments by COB August 22, 2016.

If you have any questions, call me, at (240) 402-5834 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,

Kristine F. Leahy -
S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2016.07.13 12:05:01 -04'00'

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



NDA 209115

INFORMATION REQUEST

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, and received June 24, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rucaparib, 200mg and 300mg, tablets.

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

Facilities:

1. You should list in the submission and 356H form, the required facilities information for (b) (4) site that manufactured, and performed release and stability testing for most of the submission batches.

Please respond to Facility comments by COB July 22, 2016.

Drug Process:

2. The submitted batch records are not sufficient.
 - a. Provide batch records for all of your primary stability batches.
 - b. Submit legible batch records for lots VKPM and VKPN as (b) (4) (b) (4) is not legible.
 - c. Ensure that all submitted records, including appendices and comments, have been translated into English.
3. Your pharmaceutical development report does not contain enough information to evaluate your process development supporting your process understanding and ability to reproducibly manufacture commercial lots meeting the defined CQAs of your drug product. We recommend that you summarize process development studies which were used to determine your manufacturing process parameters and operating ranges, select your in-process controls

and acceptance criteria, and demonstrate the robustness of your manufacturing process.

Include results from these studies to support your conclusions which demonstrate how drug product critical quality attributes are achieved.

Please respond to Drug Process comments by COB July 22, 2016.

Drug Product:

4. In addition to the provided components and composition of the excipients in Table 3.2.P.1-1, Table 3.2.P.1-2 and Table 3.2.P.3.2-1, include percent w/w of all ingredients present in each strength of the drug product. [REDACTED] (b) (4)
5. Explain what were the critical material attributes evaluated in [REDACTED] microcrystalline cellulose? [REDACTED] (b) (4)
6. Provide representative CoAs for the bottle and cap, and schematic drawings of the packaging components.
7. Confirm primary and site qualification stability studies listed in Section 3.2.P.8.1 were conducted using analytical methodology specified in Section 3.2.P.5.2 and were evaluated against acceptance criteria outlined in the release specification in Section 3.2.P.5.1.
8. [REDACTED] (b) (4)
9. Provide the actual sample of proposed commercial drug product that is packaged and labeled as described in the NDA.

Please respond to Drug Product comments by COB July 5, 2016.

If you have any questions, call me, at (240) 402-5864 or email: Kristine.Leahy@fda.hhs.gov.

Sincerely,

Kristine F. Leahy -S

Digitally signed by Kristine F. Leahy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2001815977,
cn=Kristine F. Leahy -S
Date: 2016.06.30 13:54:53 -04'00'

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

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/s/

KRISTINE F LEAHY
06/30/2016



NDA 209115

NDA ACKNOWLEDGMENT

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

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: rucaparib; 200 mg and 300 mg tablet

Date of Application: June 23, 2016

Date of Receipt: June 23, 2016

Our Reference Number: NDA 209115

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 August 22, 2016, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

KIM J ROBERTSON
06/29/2016

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, June 29, 2016 8:28 PM
To: jbeltman@clovisoncology.com
Subject: NDA 209115; rucaparib---Clinical Information Request

Importance: High

Hello again Dr. Beltman:

Relative to Clovis' new NDA for rucaparib, the clinical reviewer has the following request for information:

CLINICAL INFORMATION REQUEST:

- Upon review of the submitted datasets, additional information will be required for our analyses. Provide datasets in SDTM format for all ISS and ISE safety and efficacy analyses. Provide (or locate in the submission) a dataset for each study and each integrated summary that flags patients for the efficacy and safety populations.
- Provide the PDF document entitled, "bimo-co-330-010-parts-i-and-ii" and "bimo-co-330-017-parts-i-and-ii" as datasets in either SDTM or ADAM formats.

Please provide the information to address these requests to the NDA by **Tuesday, July 5, 2016, 3:30pm EST.**

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov*

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/s/

KIM J ROBERTSON
06/29/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
2525 28th Street
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rucaparib (CO-338).

We also refer to the meeting between representatives of your firm and the FDA on April 4, 2016. The purpose of the meeting was to discuss the planned content, format, and timelines for your intended NDA submission.

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 me, at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

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

Julia Beaver, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 4, 2016; 3:00-4:00 pm
Meeting Location: White Oak, Building 22, Room 1311

Application Number: IND 106289
Product Name: Rucaparib (CO-338)
Indication: Monotherapy treatment of women with ovarian cancer after two or more prior lines of treatment for tumors with germline or somatic BRCA mutation as detected by an FDA-approved test

Sponsor/Applicant Name: Clovis Oncology, Inc.

Meeting Chair: Julia Beaver, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Geoffrey Kim, MD, Director, Division of Oncology Products 1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Acting Clinical Team Leader, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Reviewer, DOP1
Harpreet Singh, MD, Clinical Reviewer, DOP1
Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP V
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Reviewer, DCP V
Roseane Charlab Orbach, PhD, Genomics Team Leader, DCP V
Robert Schuck, PharmD, PhD, Genomics Reviewer, DCPV
Erik Bloomquist, PhD, Biometrics Reviewer, DBV
Laura Fernandes, PhD, Biometrics Reviewer, DBV
Jing Li, PhD, Biopharmaceutics Reviewer, ONDP
Todd Palmby, PhD, Pharmacology/Toxicology Supervisor, DHOT
Haw-Jyh Chiu, PhD, Pharmacology/Toxicology Reviewer, DHOT
Xiao-Hong Chen, PhD, Pharmaceutical Assessment Lead, ONDP
Hisani Madison, PhD, MPH, Regulatory Scientist, CDRH/OIR/DMGP
Jeffrey Seidman, PhD, MPH, Regulatory Scientist, CDRH/OIR/DMGP
Robert Becker Jr., MD, PhD, Chief Medical Officer, CDRH
Eunice Lee, PhD, Branch Chief, CDRH/OIR/DMGP/MPCB.
William Pierce, PharmD, Associate Director for Labeling, DOP1
Amy McKee, MD, Clinical Team Leader, DOP1

Alice Kacuba, RN, MSN, RAC, Chief Project Management Staff, DOP1
Claire Myers, Regulatory Project Manager, DOP2
Kristine Leahy, RPh, Regulatory Business Process Manager, ONDP
Jeannette O'Donnell, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Jerlyn Sue Beltman, PhD, Director of Regulatory Affairs
Heidi Johanna Giordano, MA, MBA, Senior Director, Clinical Science
Sandra Malou Goble, Senior Manager, Biostatistics
Lara Maloney, Director, Clinical Science
Hanna Cho, PhD, Manager, Regulatory Affairs
Kathy Crankshaw, Senior Director, Project Team Leader
Jim Xiao, PhD, Associate Director, Clinical & Nonclinical Pharmacology
Thomas Hardingm, PhD, Senior Vice President, Preclinical Research & Translational Medicine
Gillian C. Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lindsey Rolfe, MBChB, Chief Medical Officer & Executive Vice President

1.0 BACKGROUND

The purpose of this meeting is to discuss the planned content, format, and timelines for the initial rolling NDA for accelerated approval of rucaparib. Rucaparib is a small-molecule PARP inhibitor in development for the treatment of women with advanced ovarian cancer. The Clovis is seeking accelerated approval for rucaparib as monotherapy treatment of advanced ovarian cancer in patients with BRCA-mutated tumors (inclusive of both germline and somatic BRCA mutations) who have been treated with two or more prior lines of chemotherapy. BRCA-mutated tumors are defined by the presence of a deleterious mutation in BRCA1 or BRCA2 as detected by the proposed CoDx test, a NGS-based tumor tissue test developed in collaboration with Foundation Medicine, Inc.

FDA designated rucaparib as an Orphan Drug in July 2012 and granted Breakthrough Therapy Designation in April 2015.

Key studies addressing the safety and efficacy of rucaparib in patients with advanced ovarian cancer and a BRCA mutation (BRCA^{mut}) include Study 10 and ARIEL2 (CO-338-017). Patients included in Study 10 and ARIEL2 were identified as having BRCA^{mut} either by local testing (to be followed by central confirmation) or by the proposed CoDx test. In support of the clinical studies submitted for accelerated approval, ARIEL3 is planned as a confirmatory study and to support a second ovarian indication in the maintenance setting, and ARIEL4 is planned as a second confirmatory study in the treatment setting.

The primary efficacy population will be comprised of 106 patients with BRCA mutations pooled for analysis from Study 10 Part 2A, ARIEL2 Part 1, and ARIEL2 Part 2. This group of 106 patients includes 7 patients with BRCA^{mut} that will not be included in the initial CoDx test. The primary efficacy analysis is based on ORR. The integrated safety population will include data from all 409 patients who received the recommended dose of 600 mg BID in Study 10, ARIEL2, and RUCAPANC.

Study 10 (CO-338-010) is a 3-part, single-arm, open-label Phase 1/2 study evaluating rucaparib as oral monotherapy. Part 1 evaluated escalating doses of rucaparib and identified 600 mg BID as the recommended starting dose for subsequent trials. Part 2 evaluated the efficacy of rucaparib in relapsed, high-grade ovarian cancer associated with a BRCA mutation. Part 2A enrolled patients with relapsed, platinum-sensitive disease who received 2-4 prior treatment regimens and were known to harbor a gBRCA^{mut} based on results from local testing. Clovis is requesting tissue to retrospectively confirm these BRCA mutations using the proposed CoDx test. Part 2B is enrolling advanced ovarian cancer patients who received ≥ 3 prior chemotherapy regimens and have either a gBRCA^{mut} or sBRCA^{mut}. All BRCA mutations are confirmed using the proposed CoDx test. Part 3 is characterizing the PK, including the effect of food, of a higher dose strength (300 mg) rucaparib tablet in advanced solid tumor patients with a BRCA^{mut}. In Part 3, all tumor BRCA mutations are confirmed using the proposed CoDx test.

ARIEL2 (CO-338-017) is a 2-part, open label Phase 2 study of oral monotherapy rucaparib in relapsed, high-grade ovarian cancer patients designed to identify ovarian cancer patients that are likely to respond to rucaparib. Patients are prospectively classified into 3 molecularly-defined homologous recombination deficiency (HRD) subgroups, including tBRCA^{mut} (inclusive of both germline and somatic BRCA mutations), (b) (4) and biomarker negative, by the proposed CoDx test. (b) (4)

ARIEL3 is a blinded, Phase 3 study of rucaparib vs. placebo as maintenance therapy in women with advanced ovarian cancer and is intended to serve as the confirmatory study for full approval of rucaparib. Enrollment is anticipated to be complete in the second quarter of 2016.

ARIEL4 is a planned study, not yet open to accrual: a Phase 3 trial of rucaparib vs. standard chemotherapy in women with at least two prior lines of therapy for advanced ovarian cancer with BRCA^{mut} (b) (4) disease, and includes cisplatin as a control treatment option for women with platinum-sensitive disease.

FDA sent Preliminary Comments to Clovis Oncology on March 29, 2016, to facilitate the meeting discussion.

2.0 DISCUSSION

Question 1

Clovis intends that the efficacy population for the proposed New Drug Application (NDA) will be composed of 106 ovarian cancer patients with a breast cancer gene (BRCA) mutation pooled for analysis from Study 10 Part 2A, ARIEL2 Part 1, and ARIEL2 Part 2, as depicted in Figure 3. All patients will have received ≥ 2 prior chemotherapy regimens; for patients that received only 2 prior regimens, both were platinum-based. All 106 patients have been enrolled. Currently, efficacy data as assessed by the investigator indicate a confirmed objective response rate (ORR) of 53% (56/106), and a median duration of response (DOR) of 9.2 months. In addition, 2 patients are ongoing with an initial response that is pending confirmation, thus the confirmed ORR in the NDA submission may be slightly higher. Consistent with discussion during the

Type B Breakthrough Therapy Multidisciplinary meeting held on August 20, 2015, Clovis believes that 106 patients with an anticipated ORR of approximately 50% is appropriate and adequate for accelerated approval.

Does the Agency agree that the planned patient population of 106 patients and the anticipated ORR of approximately 50% is appropriate and adequate for accelerated approval?

FDA Response: Yes; however, final determination of the suitability of the application will be a review issue that takes into consideration the totality of the submitted data.

Meeting Discussion: None.

Question 2

The Integrated Summary of Effectiveness (ISE) is planned to include data from 106 BRCA^{mut} patients who received ≥ 2 prior chemotherapy regimens. Patients will be pooled for analysis from Study 10 and ARIEL2. An overview and statistical plan for the ISE is provided in this briefing book (see Section 5.3 and Appendix 5).

Does the Agency agree that the planned ISE is appropriate for inclusion in the NDA and is adequate to support the proposed indication?

FDA Response: Yes.

Meeting Discussion: None.

Question 3

The Integrated Summary of Safety (ISS) is planned to include data from approximately 409 patients who received the recommended dose of 600 mg BID rucaparib. Patients will be pooled for analysis from Study 10, ARIEL2, and CO-338-023 (RUCAPANC, a Phase 2 study of rucaparib in patients with pancreatic cancer and a known deleterious BRCA mutation). Safety analyses will be presented for all patients with ovarian cancer as well as for all patients with other tumor types. In addition, safety analyses will be presented separately for patients with BRCA^{mut} ovarian cancer as well as for patients with gBRCA^{mut} cancer. An overview and statistical plan for the ISS is provided in this briefing book (see Section 5.4 and Appendix 6).

Does the Agency agree that the planned ISS is appropriate for inclusion in the NDA and is adequate to support the proposed indication and recommended dose?

FDA Response: Yes.

Meeting Discussion: None.

Question 4

Narratives for all deaths, serious adverse events (SAEs), and adverse events (AEs) that lead to discontinuation of study drug, as well as for adverse events of special interest (specifically, development of secondary malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) will be included as part of the overall safety analysis for the NDA. As of February 10, 2016, 2 events of MDS and 2 events of AML have been reported in Clovis-sponsored studies evaluating rucaparib. The 2 events of AML occurred in Study CO-338-014 (ARIEL3), an ongoing blinded placebo-controlled study monitored by an Independent Data Monitoring Committee (IDMC). (b) (4)

In the interest of keeping ARIEL3 blinded until study completion, unblinding of selected patient narratives will be included in the ISS. Narratives planned for inclusion in the NDA are outlined in this briefing book (see Section 5.4.1).

Does the Agency agree that narratives planned for inclusion are appropriate given the overall safety profile for rucaparib, and that inclusion of select narratives from ARIEL3 in the absence of an overall safety summary from that study is appropriate due to the fact that the study is blinded?

FDA Response: Yes. Upon analysis of the NDA submission, further patient narratives may be required in response to information requests.

Meeting Discussion: None.

Question 5

The Phase 1 (Part 1) portion of Study 10 included serial electrocardiogram (ECG) monitoring and an independent review in order to assess the effect of escalating doses of rucaparib (40 mg once daily (QD) to 840 mg BID) on corrected QT interval (QTc), as summarized in Section 5.5.1. The primary endpoint for analysis of QTc was change from Baseline (Day-1 prior to cycle 1) in QTcF (dQTcF). The secondary endpoint for analysis of QTc was change from Baseline in QTcB (dQTcB). A total of 55 patients were evaluable. No patient had a QTc >500 msec. At the dose of 600 mg BID, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec. Outlier values of QTc and change of QTc, as well as emergent morphology findings, were minimal. No arrhythmia-associated SAEs have been observed in clinical studies with oral rucaparib. As such, Clovis is not planning any further investigation of QTc.

Does the Agency agree that based on the results of the ECG analysis and the lack of arrhythmia-associated SAEs that no further investigation of QTc is required?

FDA Response: This issue is still currently under review. We will respond at the time of the Sponsor meeting.

FDA Response [provided at meeting]: Yes, we agree that no further QT assessment study is required. It appears that rucaparib has a small effect on QTc at the therapeutic dose. If it is possible, using rucaparib with drugs known to prolong the electrocardiogram QT interval should be avoided. Submit the following items for our further review once they are available:

- a. Electronic copy of the study report(s) for Study 10 and any other clinical studies of the effect of product administration on the QT interval that have been performed
- b. Electronic or hard copy of the clinical protocol
- c. Electronic or hard copy of the Investigator's Brochure
- d. Annotated CRF
- e. A data definition file which describes the contents of the electronic data sets
- f. 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
- g. 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).
- h. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- i. 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
- j. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.
- k. A completed Highlights of Clinical Pharmacology Table

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.

Further Meeting Discussion:

The Sponsor will submit the above QT related information with the NDA.

Question 6

Clovis intends that the confirmatory study, ARIEL4 “A Phase 3 Multicenter, Open-label, Randomized Study of Rucaparib versus Chemotherapy in Patients with BRCA-mutant or (b) (4) Relapsed, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer”, will be conducted as an international study. As such, input from the European Medicines Agency (EMA) and key investigators in multiple regions, as well as advice from FDA, was taken into consideration when finalizing the study design. The ARIEL4 study has been modified to incorporate all input received. A key change to the ARIEL4 study includes the addition of a platinum comparator for patients who are platinum-sensitive, defined as disease progression ≥ 12 months after last dose of most recent platinum. Clovis believes that the modified design will serve to confirm rucaparib benefit against standard treatments for ovarian cancer. The revised protocol synopsis is included in Appendix 11.

Does the Agency agree that ARIEL4, “A Phase 3 Multicenter, Open-label, Randomized Study of Rucaparib versus Chemotherapy in Patients with BRCA-mutant (b) (4) Relapsed, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer” as described in the revised protocol synopsis included in Appendix 11 is appropriate to confirm a treatment benefit in the proposed target patient population?

FDA Response: Yes; however, PFS is subject to assessment bias in open-label trials. We therefore recommend that you perform a blinded independent central review audit of scans using both NCI and PhRMA audit methodologies (Dodd et. al., Biometrics 2011 and Amit et. al., EJC 2011). The decision on whether to use either the PhRMA or NCI approach as the primary method is up to you. However, please note that it would be difficult to interpret the results if the two methods reach inconsistent conclusions. As presented at the July 2012 ODAC meeting, some clinical trials with possible investigator assessment bias were picked out for complete blinded independent central review by the NCI method but not by the PhRMA method. Further feedback may be provided upon full review of the clinical protocol.

In addition, for accelerated approval, FDA has stated that the confirmatory trial should be underway if not fully accrued. The Agency currently views both ARIEL3 and ARIEL4 to be potential confirmatory studies. At the time of NDA submission provide an explanation of how you anticipate accrual to ARIEL4 to complete if rucaparib is approved under accelerated approval.

Include sparse PK sampling in all, or the majority of the patients who will receive rucaparib in the ARIEL4 trial to allow for continued exposure-response analyses for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled “*Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications*” found at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Clovis Response [submitted April 3, 2016]:

(b) (4)

Meeting Discussion:

(b) (4)

Question 7

Study data tabulation datasets (SDTM), analysis datasets (ADaM) and associated define files for Studies 10, ARIEL 2, and RUCAPANC will be provided. In addition, the ADaM dataset and a define file for each of the integrated analyses, integrated summary of safety (ISS) and integrated summary of effectiveness (ISE), will be provided. Statistical Analysis System (SAS) programs for the tables, listings and graphs based on the ADaM datasets will also be provided. Separate SAS programs will be provided for the individual study reports, and the integrated analyses. All data sets and SAS programs will be provided with the initial NDA submission. For the 60-day data update, only output tables and output graphs with a side-by-side comparison of results from initial submission compared to the updated data results will be provided, but no additional or updated datasets.

Does the Agency agree that the proposed datasets to be provided as part of the initial NDA submission are adequate?

FDA Response: Yes this is appropriate for the initial NDA; however, the updated SDTM and ADaM datasets should be submitted in your safety update (See also Response to Question 17).

Meeting Discussion: None.

Question 8

The rucaparib clinical development program has used immediate release tablets of increasing dosage strength, beginning with 40 and 60 mg, then 120 mg, and currently 200 and 300 mg. The excipient profiles for each of these dosage forms (b) (4) The pharmacokinetics (PK) of oral rucaparib has been characterized in Study 10. Specifically, an intensive PK profile of the 600 mg BID dose is available for the 60 mg strength tablets (Study 10 Part 1; 7 patients) and for the 300 mg strength tablets (Study 10 Part 3; 26 patients). Sparse PK is available for the 60 mg, 120 mg, and 300 mg strength tablets (Study 10 Part 2 and

ARIEL2; 106 patients). No significant difference between the PK of the dosage strengths was expected based on the highly similar excipient profiles. In addition, the various dosage strength tablets have been characterized analytically, including identification, assay and degradation products by (b) (4) (b) (4) content uniformity, disintegration, and dissolution. All dose strengths were found to be (b) (4) based on these analytic properties. Moreover, based on intensive PK and population PK (PPK) analysis, no significant differences were observed among all tablet strengths. A complete summary of the dosage strength compositions and PK are included in this briefing book (see Section 5.5.2 and Appendix 7). Taken together, Clovis believes that these data support the commercial use of the 200 and 300 mg tablets.

Does the Agency agree that the completed PK and analytic studies support the clinical pooling strategy across Study 10 and ARIEL2, and the commercial use of 200 mg and 300 mg rucaparib tablets?

FDA Response: Based on our initial review of your population PK analysis, there appears to be no significant differences in exposure following 600 mg rucaparib BID using different rucaparib tablet strengths. Therefore, your proposed clinical pooling strategy across Study 10 and ARIEL2 appears appropriate. A final determination will be made at the time of NDA review. The 200 and 300 mg strengths are (b) (4) and a biowaiver request may be included in the NDA for the former.

Clovis Response [submitted April 3, 2016]:

Biowaiver request for commercial 200 mg tablet strength will be included in Section 1.12.15 of the NDA.

The following CMC information will be included in the biowaiver request to show (b) (4)
(b) (4) (b) (4)

- Rucaparib tablets (200 mg & 300 mg) are manufactured from a (b) (4) including:

(b) (4)

Does FDA agree that the above information is sufficient to support a biowaiver for the 200 mg tablet strength?

Meeting Discussion:

The information appears sufficient. However, this will be a review issue.

Question 9

A Population Pharmacokinetic (PPK) analysis entitled “Population Pharmacokinetic Analysis for Rucaparib in Studies A4991014, CO-338-010 (Study 10) and CO-338-017 (ARIEL2)” is planned for inclusion in the NDA. A summary of preliminary PPK results and an overview of the PPK

modeling plan for the NDA, including key covariates to be tested, are included in this briefing book (see Section 5.5.2 and Appendix 7).

Does the Agency agree that the planned PPK analysis is adequate and appropriate to support the proposed indication?

FDA Response: Your planned PPK analysis is reasonable; the adequacy will be determined upon review of the NDA submission.

Meeting Discussion: None.

Question 10

An exposure-response (ER) analysis entitled “Exposure-Response Analysis for Rucaparib in Studies CO-338-010 and CO-338-017” is planned for inclusion in the NDA. A summary of preliminary ER analysis results and an overview of the ER analysis plan for the NDA, including key safety and efficacy endpoints and covariates to be tested, are included in this briefing book (Section 5.5.2).

Does the Agency agree that the planned ER analysis is adequate and appropriate to support the proposed indication?

FDA Response: Your planned ER analysis is reasonable; the adequacy will be determined upon review of the NDA submission.

Meeting Discussion: None.

Question 11

Two additional clinical pharmacology studies are planned. These include:

- Study CO-338-044: [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Section 5.10.1 and Appendix 10)
- Study CO-338-045: [REDACTED] (b) (4)
[REDACTED] (Section 5.10.2)

Both study protocols have been submitted to FDA for review, and will be open to enrollment in 2016. These studies will be ongoing at the time of initial approval. Clovis commits to submit the clinical study reports for each of these two studies as a post marketing commitment.

Does the Agency agree with the timing and submission plans for the planned clinical pharmacology studies, CO-338-044 and CO-338-045?

FDA Response: The proposal appears acceptable.

Meeting Discussion: None.

Question 12

The proposed companion diagnostic (CoDx) for use with rucaparib is based on tumor tissue analysis, enabling both germline and somatic BRCA mutations to be identified. The position and identity of the BRCA alteration is determined directly using next generation sequencing (NGS), whereas the categorization of a mutation as germline or somatic is inferred using an analytically validated method. This is in contrast to the FDA-approved BRCAAnalysis CDx™ blood test, which only identifies germline BRCA mutations. In clinical trials with rucaparib, patients somatic and germline BRCA mutations had comparable response rates (see Figure 1).

Clovis believes the identification of both germline and somatic mutations to be an important aspect of the CoDx, and therefore the use of the terms germline and somatic in labeling are appropriate for the types of mutations detected by the CoDx and critical to the safe and effective use of rucaparib. Clovis proposes that germline and somatic BRCA mutations be specified in Section 1 (indication) and Section 14 (clinical studies) of the rucaparib drug label. A target product profile (TPP) including the proposed use of these terms is provided in the briefing book (Appendix 2).

Does the Agency agree that the terms germline and somatic are appropriate for inclusion in Section 1 and Section 14 of the drug label?

FDA Response: This will be a review issue at the time of labeling based on data in the NDA and PMA submission. If this claim is desired, you should submit data to validate that the companion diagnostic will distinguish between germline and somatic mutations.

Clovis Response [submitted April 3, 2016]:

(b) (4)

(b) (4)

Does FDA agree with the Clovis proposal?

Meeting Discussion:

FDA reiterated that this would be a review issue.

Question 13

Clovis has developed an

(b) (4)

(b) (4)

Does the Agency agree that the proposed

(b) (4)

(b) (4)

(b) (4)

FDA Response: No.

(b) (4)

(b) (4)

Clovis Response [submitted April 3, 2016]:

Clovis understands and agrees that all AE events (serious and non-serious; all CTCAE grades) should be included.

Clovis understands that the ADRs included in section 6 of the label will be a review issue.

Meeting Discussion:

No meeting discussion.

Question 14

(b) (4)

Question 15

Clovis is planning a rolling NDA submission of 3 reviewable units (nonclinical, CMC, and clinical) in Q2 2016. An overall rolling NDA plan, including contents and timing, is included in this briefing book (Figure 2, Table 1, and Appendix 3). A comprehensive table of contents (TOC) of the initial NDA supporting accelerated approval is provided in this briefing book as an appendix.

Proposed Contents and Timeline for Rolling NDA Submission

Reviewable Unit (eCTD Modules)	Planned Submission Date
Reviewable Unit #1: Nonclinical and Administrative Information - Module 1 - Cover letter, Form 356h, Form 3397 (fee waived - Orphan Designation) - Exclusivity Claim (1.3.5.3) - Module 2 - Nonclinical Overview (2.4) - Nonclinical Written and Tabulated Summaries (2.6) - Module 4 - All final Nonclinical Study Reports	Week of 11 April 2016
Reviewable Unit #2: Chemistry, Manufacturing and Controls and Administrative Information	Week of 16 May 2016

• Module 1 - o Cover Letter, Form 356h - o Categorical Exclusion of ERA Statement (1.12.14) - o Patent Certification and Disclosure (1.3.5.1) - o Proprietary Name Request (1.18) • Module 2 - o Quality Overall Summary (2.3) • Module 3 - o Drug Product (3.2.P) - o Drug Substance (3.2.S) - o Appendices (3.2.A)	
Reviewable Unit #3 and Initial Application: Clinical and Administrative Information • Module 1 - o Cover Letter, Form 356h, Form 3674 - o Transfer of Obligations (1.3.1.4) - o Debarment Certification (1.3.3) - o Financial Certification and Disclosure (1.3.4) - o Draft Labeling (1.14.1) - o Risk Management Plan (non-REMS) (1.16.1) • Module 2 - o Clinical Overview (2.5) - o Clinical Summaries (2.7) • Module 5 - o Integrated Summaries of Safety and Efficacy (5.3. and 5.4) - o Clinical Study Reports (including BIMO-required Summary Level Clinical Site Datasets) - o BRCA Mutation Test Report (patient level local and central BRCA test results) (5.3.5.3)	31 May 2016
Late Component (submitted within 30 days of final unit/initial application): • Contents will be proposed and discussed during a Type B, CMC meeting planned for 20 April 2016	30 June 2016
60-day Update Safety and Efficacy Update • Module 2 - o Clinical Summaries (2.7) • Module 5 - o Integrated Summaries of Safety and Efficacy (5.3. and 5.4)	29 July 2016

eCTD = electronic common technical document; ERA = Environmental Risk Assessment;
REMS = Risk Evaluation and Mitigation Strategy

Does the Agency agree that the planned content and organization are appropriate and adequate for a rolling NDA supporting accelerated approval?

FDA Response: No, we cannot agree to this prior to your pre-NDA CMC meeting. You have not yet applied for rolling review. See Response to Question 16.

Clovis Response [submitted April 3, 2016]:

Request for a rolling NDA review was submitted on March 31 as Serial Number 192

Overall rolling submission timeline

- Timing for Clinical Unit is gated on data maturity. All efficacy data will be included in the May 31 submission.
- Timing for Nonclinical unit is week of April 11.
 - No nonclinical questions are included today nor for upcoming CMC meeting
- Timing for CMC unit is gated by CMC discussion (to be held April 20).

Does FDA agree that the nonclinical module may be submitted during the week of April 11, and that the Clinical module with all efficacy data at the end of May?

Meeting Discussion:

The proposed time line for rolling submission of the non-clinical and clinical modules is acceptable.

Question 16

Clovis proposes that one clinical data update will be submitted approximately 60 days following the submission of the final NDA module (Section 5.9). This data update will include additional efficacy data for the 106 patients included in the ISE. This data update will also include additional safety data for the integrated safety population (409 patients) presented in the ISS. No new patients are planned to be included in the update, but rather additional data for the patients included in the NDA will be provided. This update may also include additional confirmatory tBRCA test results for patients who submitted formalin-fixed paraffin-embedded (FFPE) tumor tissue samples retrospectively. In addition, the update will include any other information agreed upon with the Agency.

Does the Agency agree with the content and timing for the planned data update to be submitted during the NDA review cycle?

FDA Response: No. We do not recommend that you submit an application until the efficacy data is mature. We do not recommend an updated efficacy submission unless requested specifically by us during the review. It is acceptable to submit your 120 day safety update by day 60 if you wish. You also may submit additional confirmatory tBRCA at 60 days.

Clovis Response [Submitted April 3, 2016]:

Clovis believes that the efficacy data will be sufficiently mature at the time of NDA submission, and agrees that an efficacy update will not be required.

Proposed content to be included in the 60-day update:

- Safety data update
- Additional BRCA results
 - These results will be from patient samples collected retrospectively in Study 10 Part 2A.

- o BRCA results from ARIEL2 will be complete at the time of original submission.

(b) (4)

Does FDA agree that above content are appropriate and adequate for the 60-day update?

Meeting Discussion:

The proposed content is acceptable and may be submitted at 60 days.

Question 17

Clovis intends to submit Bioresearch Monitoring (BIMO) Clinical Data as requested. These data will be limited to the pivotal studies Study 10 (CO-338-010) and ARIEL2 (CO-338-017). The BIMO data will not cover the studies, A4991014 (Phase 2 dose escalation and combination study) or RUCAPANC (CO-338-023).

Does the Agency agree that BIMO data for Studies Study 10 and ARIEL2 is adequate?

FDA Response: Yes.

Meeting Discussion: None.

Question 18

Rucaparib for tBRCA^{mut} ovarian cancer was granted Breakthrough Therapy Designation (BTD) on April 03, 2015 based on data indicating that rucaparib had the potential to provide significant improvement over existing therapies for the treatment of a life-threatening condition. By the criteria described in the draft Guidance for Industry entitled “*Expedited Programs for Serious Conditions – Drugs and Biologics*”, Clovis proposes that the planned NDA merits priority review designation. As such, Clovis plans to request priority review at the time of NDA submission.

Does the Agency intend to conduct an expedited review of the NDA and agree that a priority review designation is appropriate for inclusion in the planned NDA?

FDA Response: This will be a review issue and will be determined at the time of filing.

Meeting Discussion: None.

Question 19

Within the meeting minutes for a Type B meeting held on 20 August 2015, FDA requested that Clovis submit a Pediatric Study Plan (PSP) for rucaparib. However, the Pediatric Research Equity Act (PREA) states that “Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526.” Rucaparib was granted Orphan Drug Designation for the treatment of ovarian cancer in July 2012 (Designation # 12-3747). Therefore, Clovis believes that a PSP for rucaparib is not required at this time.

Does the Agency agree that a PSP is not required?

FDA Response: Yes. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), your orphan drug designation exempts you from this requirement. Please be sure to include the information for your orphan drug designation in your NDA application.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

Clovis will provide at day 60 the following additional information to their NDA:

- Safety data update
- Additional BRCA results
 - These results will be from patient samples collected retrospectively in Study 10 Part 2A.

(b) (4)

In addition, we note that a chemistry pre-submission meeting is to be held on April 20, 2016. We refer you to the minutes of that meeting for any additional agreements that may be reached.

PREA REQUIREMENTS

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

PRESCRIBING INFORMATION

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

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

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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

Office of Scientific Investigations (OSI) Requests

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

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

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

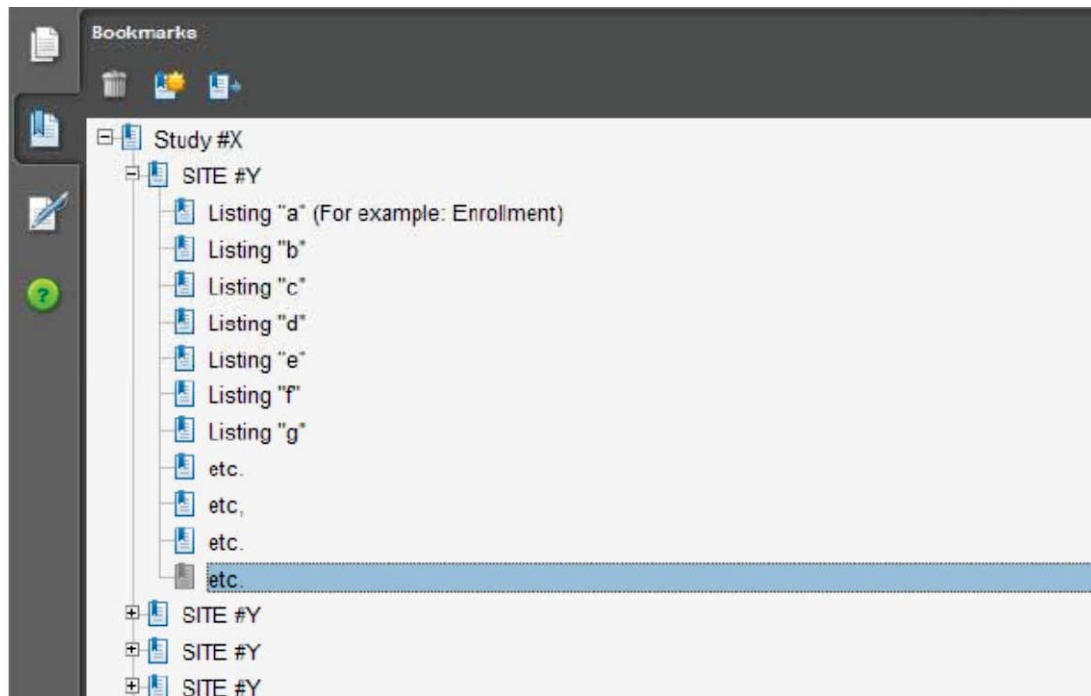
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



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

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

References:

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Pre-NDA CMC meeting to be held on April 20, 2016.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor to submit requested QT information with the NDA. See Question 5	Sponsor	With NDA submission

6.0 ATTACHMENTS AND HANDOUTS

See attached Sponsor slides

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/s/

JEANNETTE L DININ
04/15/2016

JULIA A BEAVER
04/15/2016



IND 106289

MEETING PRELIMINARY COMMENTS

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Director Regulatory Affairs
499 Illinois Street Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

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

We also refer to your February 10, 2016 correspondence, received February 10, 2016, requesting a meeting to present and gain agreement on the planned content for the CMC unit of the rolling NDA for accelerated approval of Rucaparib.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Kristine Leahy, RPh., at (240) 402-5834.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief (Acting), Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: CMC

Meeting Date and Time: April 20, 2016, 2:00P.M. – 3:00P.M. Eastern Time
Meeting Location: White Oak Building 22 Room 1315

Application Number: 106289
Product Name: Rucaparib
Indication: Treatment of advanced (b) (4) Ovarian cancer)
Sponsor Name: Clovis Oncology, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 20, 2016, 2:00P.M. – 3:00P.M. Eastern Time, at the FDA, Building 22, Room 1315 between Clovis Oncology, Inc. and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory business process manager (RBPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact Kristine Leahy, if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to present and gain agreement on the planned content for the CMC unit of the rolling NDA for accelerated approval of rucaparib.

Preliminary comments are being sent to the sponsor April 13, 2016.

2.0 DISCUSSION

Question 1:

Does the Agency agree that the proposed stability data to be included in the application is adequate to qualify (b) (4) as the dosage form manufacturing site?

FDA Response to Question 1:

The proposed stability data package appears to be reasonable to qualify (b) (4) as the dosage form manufacturing site. However, the final determination will be made during the NDA review.

Question 2:

Does the Agency agree that it is acceptable to submit the 3 month data from the (b) (4) stability lots in the planned 30-day update?

FDA Response to Question 2:

Yes, it is acceptable to submit the 3 month long term stability data in the planned 30-day update. Provide clarification why the 3 month data point for long term stability data will not be available at the time of submission.

Question 3:

(b) (4)

(b) (4)

Does the Agency agree that the test attributes provided in these commercial rucaparib drug product specifications are adequate and appropriate as commercial drug product specifications?

FDA Response to Question 4:

The test attributes provided in commercial rucaparib drug product specifications appear to be reasonable. However, regarding (b) (4) control of the drug substance in the drug product, add a test attribute in the drug product specifications at release and stability, or provide justification as to why it is not necessary.

Question 5:

Does the Agency agree that it is acceptable to submit the (b) (4) month (b) (4) storage data from the third drug substance lot in the planned 30-day update?

FDA Response to Question 5:

Yes, we agree that it is acceptable to submit the (b) (4)-month (b) (4) storage data from the third drug substance lot in the planned 30-day update.

Question 6:

Does the Agency agree that the test attributes included in these commercial rucaparib drug substance specifications are adequate and appropriate as commercial drug substance specifications?

FDA Response to Question 6:

We recommend that you include a test and an appropriate acceptance limit for (b) (4) in the commercial drug substance specification. Include D_{10} and D_{50} particle size specifications in addition to the D_{90} specification already proposed or provide justification for lack of these specifications in your NDA submission. We remind you that your proposed impurities limits, particularly for specified impurity (b) (4), should be in line with the release and stability data provided upon NDA submission. The final evaluation of the drug substance specification is a review issue and will be based on the information provided in the NDA submission.

Question 7:

Does the Agency agree with the conclusion that rucaparib qualifies for Categorical Exclusion from an Environmental Assessment?

FDA Response to Question 7:

The applicant responded to the Agency's questions discussed during the 02 November 2015 Type B CMC meeting. The submitted information addresses the embryo-fetal development toxicology of rucaparib in rats, the potential estrogenic, androgenic, or thyroid hormone pathway activity for rucaparib, MOA and receptor binding values, and provides a literature search including available information on the potential environmental effects of other PARP inhibitors. The information appears adequate to support a conclusion that a claim of categorical exclusion under 21 CFR 25.31(b) is appropriate for this drug application. As agreed, the summarized data will also be provided in the NDA (eCTD 1.12.14.). The final determination will be made during the NDA review.

ADDITIONAL FDA COMMENTS

Biopharmaceutics:

We have the following comments regarding the dissolution information that should be provided in your NDA for the proposed (b) (4), 200 mg, and 300 mg Rucaparib immediate release tablets.

I. Dissolution Method:

(b) (4)

(b) (4)

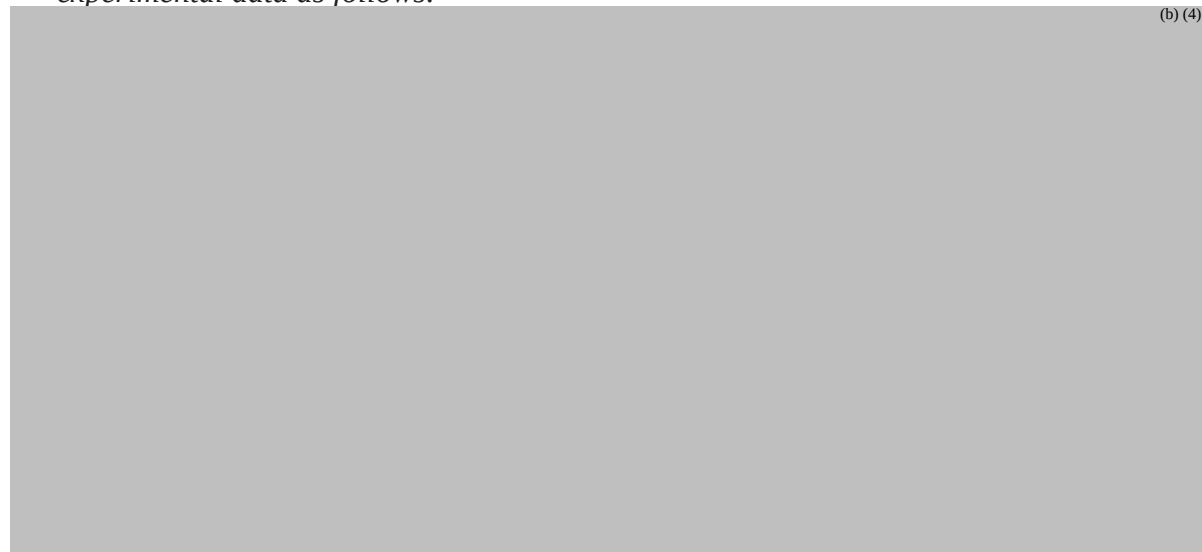
II. Dissolution Acceptance Criterion: *For the selection of the dissolution acceptance criterion (a) of your product, the following points should be considered:*

- a. *The dissolution profile data (i.e., 15, (b) (4) and (b) (4) min) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) should be used for setting the dissolution acceptance criterion (a) of your product.*
- 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 occurs.*

- c. *The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).*
- d. *The selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs.*
- e. *A detailed discussion of the justification of the proposed dissolution acceptance criterion should be included in the appropriate section of the CTD.*

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

(b) (4)



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/s/

KRISTINE F LEAHY
04/13/2016

ANAMITRO BANERJEE
04/13/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 106289

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Clovis Oncology, Inc.
499 Illinois Street
Suite 230
San Francisco, CA 94158

ATTENTION: Jeri Beltman, PhD.
Director, Regulatory Affairs

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rucaparib Tablets, 200mg and 300mg.

We also refer to your December 10, 2015, correspondence, received December 10, 2015, requesting review of your proposed proprietary name, Rubraca.

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

A request for proprietary name review for Rubraca should be submitted once the NDA is submitted.

If any of the proposed product characteristics as stated in your December 10, 2015, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/03/2016



IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Director, Regulatory Affairs
499 Illinois Street, Suite 230
San Francisco, CA 94158

Dear Dr. Beltman:

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

We also refer to the meeting between representatives of your firm and the FDA on November 2, 2015. The purpose of the meeting was to discuss development and manufacturing strategic plans for both drug substance and drug product.

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 Rabiya Laiq, Pharm.D, Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes & Sponsor Slides



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC

Meeting Date and Time: November 2, 2015 2:00 PM-3:00 PM
Meeting Location: CDER/WO/Bldg.22/Rm.1313

Application Number: IND 106289
Product Name: Rucaparib
Indication: Treatment of Advanced (b) (4) ovarian cancer)
Sponsor: Clovis Oncology, Inc.

Meeting Chair: Olen Stephens, Ph.D.
Meeting Recorder: Rabiya Laiq, Pharm.D.

FDA ATTENDEES

Olen Stephens, Quality Drug Product Branch Chief (Acting)
Xiao-Hong Chen, Quality Drug Product Lead (Acting)
James Laurenson, EA Reviewer
Haw-Jyh (Brian) Chiu Pharm/Tox Reviewer
Palmby, Todd, Pharm/Tox Lead
Monica Cooper, API Reviewer
Rabiya Laiq, Regulatory Business Process Manager (RBPM)

SPONSOR ATTENDEES

Jeri Beltman, PhD, Director, Regulatory Affairs
Hanna Cho, PhD, Manager, Regulatory Affairs
Jeff Etter, PhD, Vice President, Pharmaceutical Development
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President
Robert Tengler, Associate Director, Pharmaceutical Development
(b) (4)

1.0 BACKGROUND

The purpose of meeting was to discuss development and manufacturing strategic plans for both drug substance and drug product. FDA sent Preliminary Comments to Clovis on October 28, 2015.

2. DISCUSSION

Question 1:

Does the Agency agree that the proposed stability data are adequate to qualify the

(b) (4)

(b) (4)

FDA Response to Question 1:

No, we do not agree. Your proposal to provide

(b) (4)

(b) (4)

is not adequate

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Sponsor's Response to Question 1: Refer to slide deck attached.

Meeting Discussion:

The FDA and sponsor are in agreement with regards to the data necessary to support manufacturing the 200 mg to 300 mg tablets at the (b) (4) manufacturing site. This data will include 3 months accelerated stability data from one batch of each strength, submitted with the original Module 3 submission. Additional stability data may be submitted, but FDA does not commit to reviewing this data if it arrives after the initial 30 days of the NDA review clock.

(b) (4)

Sponsor's Response to Question 2: Refer to slide deck attached.

Meeting Discussion:

(b) (4)

Question 3:

Does the Agency agree that the (b) (4) is acceptable as the GMP starting material for the manufacture of rucaparib camsylate drug substance?

Sponsor's Response to Question 3: Refer to slide deck attached.

FDA Response to Question 3:

No, we do not agree because you have not shown that the proposed starting material specification would be applicable to other routes of synthesis.

To support your proposal of (b) (4) as the

(b) (4)

(b) (4)

Sponsor's Response to Question 3: Refer to slide deck attached.

Meeting Discussion:

The sponsor acknowledged the need for additional data to support designation of (b) (4) as the starting material. The sponsor will provide the following data to support designation of (b) (4) as a starting material:

- 1) Alternative synthetic routes to the starting material.
- 2) Potential impurities arising from these alternative routes.
- 3) Data to demonstrate that their analytical methods will detect and control potential impurities.
- 4) Data from impurity (b) (4) studies.
- 5) Proposed specification limits for the starting material including limits for potential impurities.

The sponsor will submit this data in a request for response to the IND.

Question 4:

Does the Agency agree with the conclusion that rucaparib qualifies for Categorical Exclusion from an Environmental Assessment?

Sponsor's Response to Question 4: Refer to slide deck attached.

FDA Response to Question 4:

The Agency requires additional information before making this determination. Although the NDA appears to qualify for a categorical exclusion in accordance with 21 CFR 25.31(b), the data from the previously conducted embryo-fetal development toxicology study of rucaparib in rats and relatively high production volume raises questions about rucaparib residues in the environment and potential toxicity to environmental organisms. In addition, FDA recently published a draft environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid hormone pathway activity (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf>). In light of this information, please provide further justification for the claim of categorical exclusion and required statement of no extraordinary circumstances (see 21 CFR 25.15(a) and 25.21).

Meeting Discussion:

The sponsor requested feedback regarding the claim for categorical exclusion for this application. The sponsor's response to FDA's preliminary answer to Question #4 addressed rucaparib's structure, receptor screening assays, nonclinical toxicology, and production data. The response appears reasonable. The sponsor argued that rucaparib's structure is distinct from that of estrogen, progesterone, androgen, and triiodothyronine. The sponsor also noted the lack of significant androgenic and estrogenic receptor inhibition. The Agency noted that other structures could still have estrogenic, androgenic, or thyroid effects, and also recommended providing the actual receptor binding values. The Agency also recommended a literature search about non-involvement in the estrogenic, androgenic, and thyroid pathways, including any available data on the potential environmental effects of other PARP inhibitors. This would need to be a part of the environmental analysis submitted to eCTD 1.12.14.

The sponsor will summarize their data on rucaparib as it pertains to the request for a categorical exclusion from environmental assessment. The sponsor will submit this summarized data to the IND in a request for written response regarding the adequacy of this justification. The summarized data will also be provided in the NDA.

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/s/

RABIYA LAIQ
11/19/2015

OLEN M STEPHENS
11/19/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106289

MEETING MINUTES

Clovis Oncology
Attention: Jeri Beltman, PhD
2525 28th Street
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rucaparib (CO-338).

We also refer to the meeting between representatives of your firm and the FDA on August 20, 2015. The purpose of this multi-disciplinary breakthrough therapy meeting was to discuss confirmatory trial studies and your plans to request accelerated approval.

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 me, at (240) 402-4978 or email:
Jeannette.Odonnell@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Multi-Disciplinary Breakthrough Therapy Meeting

Meeting Date and Time: August 20, 2015; 10:00-11:00 am
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: IND 106289
Product Name: Rucaparib (CO-338)
Indication: Rucaparib is indicated as monotherapy treatment of advanced ovarian cancer in patients with deleterious or suspected deleterious BRCA-mutated tumors (inclusive of both germline and somatic BRCA mutations) (b) (4) as detected by an FDA-approved test, and who have been treated with two or more prior lines of chemotherapy.

Sponsor/Applicant Name: Clovis Oncology

Meeting Chair: Amy McKee
Meeting Recorder: Jeannette O'Donnell

FDA ATTENDEES

Geoffrey Kim, M.D., Director, Division of Oncology Products 1
Amna Ibrahim, M.D., Deputy Director, DOP1
Amy McKee, M.D., Clinical Team Leader, DOP1
Sanjeeve Balasubramaniam, M.D., Clinical Reviewer, DOP1
Shenghui Tang, Ph.D., Biometrics Team Leader, DBV
Laura Fernandes, Ph.D., Biometrics Reviewer, DBV
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
Todd Palmby, Ph.D., Pharmacology/Toxicology Supervisor, DHOT
Haw-Jyh Chiu, Ph.D., Pharmacology/Toxicology Reviewer, DHOT
Hisani Madison, PhD, MPH, Regulatory Scientist, CDRH/OIR/DMGP
Reena Philip, Ph.D, Division Director, CDRH/OIR/DMGP
Olen Stephens, PhD, Acting Branch 2 Chief, ONDP
Xiao-Hong Chen, PhD, Pharmaceutical Assessment Lead, ONDP
Jeannette O'Donnell, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Jerlyn Sue Beltman, PhD, Director of Regulatory Affairs
Heidi Johanna Giordano, MA, MBA, Senior Director, Clinical Science
Jeffrey Dean Isaacson, PhD, Senior Director, Biostatistics & Data Management
Kevin Kuanchieng Lin, PhD, Principal Scientist, Molecular Diagnostics
Sandra Malou Goble, Senior Manager, Biostatistics
Lara Maloney, Director, Clinical Science
Michal Raponi, PhD, Senior Director, Molecular Diagnostics
Gillian C. Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lindsey Rolfe, MBChB, Chief Medical Officer & Executive Vice President
Roman V. Yelensky, PhD, Vice President, Biomarker & CoDx Development

1.0 BACKGROUND

The Sponsor has requested a Type B meeting to discuss the development plan for the agent rucaparib, an oral PARP inhibitor, for the treatment of women with ovarian cancer with gBRCAm, tBRCAm, or homologous recombination deficiency as defined by a next generation sequencing panel and algorithm that are under development, in cooperation with Foundation Medicine. Based on data from clinical trials CO-338-10, "Study 10," and CO-338-17, "ARIEL2," rucaparib received Breakthrough Therapy Designation in April, 2015, for treatment of women with advanced gBRCAm or tBRCAm ovarian cancer who have progressed after at least two lines of platinum-containing chemotherapy.

As of July 2015, the RECIST ORR for patients from all trials with BRCAm tumors is 71% (56/79), including 8% (6/79) CR. For >2 or >3 prior chemotherapies, ORR is 68% and 61% respectively. These results are consistent with the data submitted for BTD (ORR 66%, 27/41).

Using the

(b) (4)

(b) (4)

(b) (4)

It is notable that the Sponsor is seeking to [REDACTED] (b) (4)

FDA sent Preliminary Comments to Clovis Oncology on August 14, 2015.

2. DISCUSSION

2.1. Clinical

(b) (4)

Meeting Discussion:

The Sponsor will continue to gather data on patients with different cutoffs and will return to discuss with the Agency at a later date.

Question 2: The ORR of 68% and 61% for tBRCA⁺ patients, who have received 2 or more, or 3 or more prior chemotherapy regimens, respectively, are within the same range, and appear to represent a “meaningful advantage over available therapies.” Does the Agency agree that patients who have received 2 or more prior chemotherapies may be an appropriate target population and indication for accelerated approval?

FDA Response: The final indication will be a review issue.

Regarding whether this is an appropriate target population, this may be possible, provided that the indication is limited to tBRCAM disease and two prior platinum-based regimens. If you wish to include patients who have received any two prior chemotherapy regimens, you must provide data that includes the prior chemotherapy regimens, including non-platinum lines of chemotherapy, in platinum-sensitive disease and justification for inclusion of this population.

Meeting Discussion:

The Sponsor proposed a marketing application for the tBRCAM population for patients who have received two prior chemotherapy regimens. The Agency emphasized that patients should have received two or more prior platinum-based doublets, but that this population is appropriate for a marketing application.

Question 3: Does the Agency agree that ARIEL4, “A Phase 3 Multicenter, Open-label, Randomized Study of Rucaparib versus Chemotherapy in Patients with BRCA-mutant or (b) (4) Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer” is appropriate to confirm a treatment benefit in the proposed target patient population?

FDA Response: No. (b) (4)

Meeting Discussion:

See meeting discussion for Question 5. The Agency clarified that the recommendation for not including the (b) (4) patients is tied to the recommendation to study this population independently.

2.2. Statistics

Question 4: Does the Agency agree that comparative design including a control arm who will be treated with a single agent non-platinum comparator, such as paclitaxel, is an appropriate design?

FDA Response: Yes.

Question 5: Does the Agency agree that the (b) (4)

FDA Response:

(b) (4)

2.3. CDRH

Question 6: Only those patients classified as HRD⁺ by the proposed CoDx, but not those classified as biomarker-negative, will be eligible for enrollment. Clovis and FMI recognize that tests used to make treatment decisions typically require an IDE. However, several modules of the PMA for the proposed CoDx will be under review at the time ARIEL4 is initiated. Does the Agency agree that a reference to the submitted PMA modules may be provided in lieu of an IDE given the anticipated PMA submission status?

FDA Response: Information provided in the ARIEL 4 clinical study synopsis appears to be consistent with a non-significant risk (NSR) study, provided that significant risk biopsy procedures are not being conducted to secure tissue specimens for the sole purpose of confirming HRD status. Significant risk procedures include (but are not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel. If significant risk procedures will not be used, the study will not require an IDE application to FDA and a reference to the submitted PMA module will not be required. Please be aware that sponsors of non-significant risk studies must comply with the abbreviated IDE requirements set forth in (§812.2(b)). <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046702.htm#resofspoof>.

Question 7

Does the Agency agree that description of the proposed CoDx test, including the final algorithm rationale and methodology, is sufficiently clear, detailed, and complete for inclusion in the PMA to be submitted in parallel with the NDA?

FDA Response: You have provided a sufficient overview of the IUO test that will be used for patient enrollment, but CDRH would like to advise that a detailed review of the proposed CoDx test (such as the algorithm rationale and methodology) will be conducted in the PMA application. CDRH has the following comments:

- Please ensure that the study dataset used in the training of the final algorithm is independent of the validation study dataset. The final assay algorithm, including the cut-off values, should be locked down prior to the initiation of clinical study and analytical validation studies.
- Please plan to provide drug efficacy analysis for each of the patient subgroups identified by the CoDx test (tBRCA (b) (4))

Question 8

Does the Agency agree that the final algorithm (based on ARIEL2 Part 1) will be considered to be prospectively applied when used to classify patients enrolled in ARIEL2 Part 2?

FDA Response: Yes.

Question 9

As clinical data on rucaparib accumulates, it may become evident that different LOH cut-offs are appropriate for different treatment settings (for example, treatment versus maintenance, or number of lines of prior therapy). Does the Agency agree that different cut-offs may be defined for different settings, prospectively included in the CoDx test, and included in labeling?

FDA Response: We do not recommend this approach, as this would lead to unnecessary confusion for patients and physicians. We recommend that you choose a cutoff that accurately predicts a patient population that would benefit from rucaparib therapy independent of disease setting.

Question 10

Does the Agency agree that the studies planned for inclusion in the initial NDA are adequate to gain accelerated approval for rucaparib for the proposed indication?

FDA Response: We encourage you to submit your initial application in the tBRCAm population. See responses to Questions 1-3 above.

Question 11

Does the Agency agree that ongoing studies may be completed and reports submitted following accelerated approval?

FDA Response: We recommend that you discuss the trials with the Agency after top-line results have been obtained prior to submitting marketing applications.

2.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog)
See: <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) See: <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the

Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm> .

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at:

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

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

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

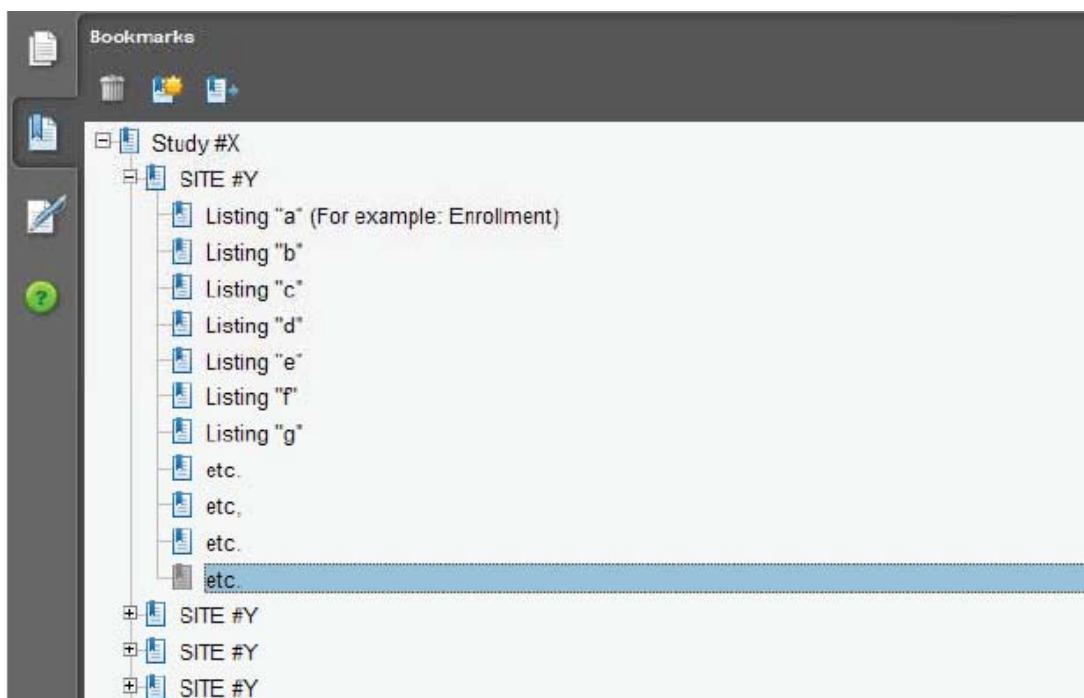
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA’s guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

JEANNETTE L O'DONNELL
08/31/2015

AMY E MCKEE
08/31/2015



IND 106289

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Clovis Oncology
Attention: Jeri Beltman, PhD
2525 28th Street
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rucaparib (CO-388).

We also refer to your February 6, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that rucaparib (CO-388) for monotherapy treatment of advanced ovarian cancer in patients who have received at least two lines of prior (b) (4) therapy, with BRCA-mutated (tBRCAm) tumors, inclusive of both germline BRCA (gBRCAm) and somatic BRCA (sBRCAm) mutations meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of rucaparib (CO-388) for monotherapy treatment of advanced ovarian cancer in patients who have received at least two lines of prior (b) (4) therapy, with BRCA-mutated (tBRCAm) tumors, inclusive of both germline BRCA (gBRCAm) and somatic BRCA (sBRCAm) mutations to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial

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

breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for rucaparib (CO-388) for monotherapy treatment of advanced ovarian cancer in patients who have received at least two lines of prior (b) (4) therapy, with BRCA-mutated (tBRCAm) tumors, inclusive of both germline BRCA (sBRCAm) and somatic BRCA (sBRCA) mutations is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

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

Sincerely,

{See appended electronic signature page}

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

²

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

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

/s/

GEOFFREY S KIM
04/03/2015

Benton, Sandra J

From: Benton, Sandra J
Sent: Tuesday, March 24, 2015 11:28 AM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Balasubramaniam, Sanjeeve; Ibrahim, Amna; Kim, Geoffrey; McKee, Amy; O'Donnell, Jeannette
Subject: RE: March 27, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 106289

As the Council agrees with DOP1's recommendation to grant Clovis Oncology's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the March 27, 2015 meeting agenda.

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

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

From: Benton, Sandra J
Sent: Wednesday, March 18, 2015 8:15 AM
To: Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V
Cc: Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Moscicki, Richard; Throckmorton, Douglas C; Balasubramaniam, Sanjeeve; Ibrahim, Amna; Kim, Geoffrey; McKee, Amy; O'Donnell, Jeannette
Subject: March 27, 2015 - Medical Policy Council – Breakthrough Therapy Designation - IND 106289

Hi! OMP has scheduled a Medical Policy Council discussion on March 27, 2015 regarding the breakthrough therapy designation request from Clovis Oncology Inc. for its IND 106289, Rucaparib for monotherapy in BRCA-mutated (b) (4) ovarian cancer patients following two prior (b) (4) regimens.

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

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

Would you please review DOP1's recommendation and let me know by COB Tuesday, March 24 if –

- You agree with DOP1's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.

- You disagree with DOP1's recommendation regarding this breakthrough therapy request.

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

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

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

<< File: Rucaparib BTB Brief MPC.DOC >> << File: Rucaparib BTB MPC.PPT >> << File: 106289 BTDR.PDF >>

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Oncology Products 1
March 27, 2015

Summary Box

1. IND 106289
2. Clovis Oncology Inc.
3. Rucaparib
4. Indication:
Monotherapy in BRCA-mutated (b) (4)-sensitive relapsed ovarian cancer patients following two prior platinum-containing regimens

5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition?

Yes.

6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints?

Yes. The overall response rate (ORR) seen with rucaparib represents a significant improvement (66% vs. 41%) over the rates reported in retrospective analyses for the third-line treatment of platinum-sensitive ovarian cancer, and is up to 50% greater than that seen in other studies. This does appear to be a significant breakthrough in efficacy for a third-line treatment for this patient population. Further, the duration of response of nearly six months at data cutoff appears promising, with median not yet reached.

Division: Division of Oncology Products 1
Medical officer: Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader: Amy McKee, MD

1. Brief description of the drug

Rucaparib selectively promotes lethality in tumor cells that lack functional BRCA proteins while sparing normal tissues that retain BRCA function (synthetic lethality). BRCA1 and BRCA2 are human genes that belong to a class known as tumor suppressors. In normal cells, BRCA proteins play a key role in homologous recombination DNA repair (HRR) of double-strand breaks (DSB), helping to maintain genomic integrity and preventing neoplastic transformation.

There is scientific evidence that PARP inhibition is expected to be an effective option for treating platinum-sensitive tumors, such as ovarian cancer, due to the DNA repair deficiencies that are associated with platinum sensitivity. PARP proteins also serve to isolate and coordinate the repair of a

different type of DNA damage, the single strand break (SSB). In the absence of PARP function, SSB convert to DSB. Preclinical studies show that BRCA-defective tumors are intrinsically sensitive to PARP inhibitors such as rucaparib, which prevent the repair of DNA SSB and subsequently induce a dependency on HRR that requires functional BRCA.

2. Brief description of the disease and intended population

Ovarian cancer is a serious and life-threatening disease. It is the fifth most common cancer in women in developed countries, with an estimated 21,290 new cases and 14,180 deaths expected in the US in 2015; from 2007 to 2011, the death rate decreased by 2.0% per year in white women and was stable in black women (American Cancer Society 2015). Initial symptoms are frequently vague and non-specific, and the majority of women have late-stage disease at diagnosis, and their prognosis is generally poor.

Women with germline BRCA mutations (gBRCAm) are predisposed to develop ovarian cancer, and up to 15% of women with ovarian cancer have a gBRCA mutation. Somatic BRCA mutations also occur within ovarian tumors at a rate of approximately 7%. In total, it is estimated that germline and/or somatic (tumor) BRCA mutations occur in 18% of all ovarian cancers and 23% of high-grade serous cancers.

Current medical practice for newly-diagnosed advanced ovarian cancer is optimal surgical debulking with the goal of reducing tumor burden to sub-centimeter or smaller residua. Surgery is then followed by chemotherapy, with the standard front-line carboplatin and paclitaxel regimen given for six 3-week cycles. After the completion of chemotherapy, the patient is assessed for recurrence or progression on a regular basis; unfortunately, recurrence occurs in 80% of cases.

The duration until ovarian cancer recurrence has been found to be associated with disease biology, including aggressiveness and responsiveness to chemotherapy, drives the selection of subsequent therapy. Patients whose tumors progress during their course of platinum-based chemotherapy are considered to have “platinum refractory” ovarian cancer, and their prognosis is dismal. For those patients whose tumors recur or progress within six months of the last date of chemotherapy administration, their disease is labeled “platinum resistant,” and the prognosis is poor, with median survival estimated to be around one year. Patients whose tumors recur or progress greater than 6 months from the date of last administration of platinum-based chemotherapy are considered to have “platinum sensitive” disease. The determination of platinum sensitivity is important, as there is a survival benefit demonstrated for additional treatment with a platinum-based doublet in the second-line, platinum-sensitive setting.

Standard treatment options for patients with platinum-sensitive, second-relapse disease includes a third platinum-based chemotherapy doublet; however, cumulative platinum (and taxane) toxicity and risk of developing platinum allergy often prompt the consideration of other standard treatment options, which include primarily single-agent cytotoxic chemotherapy. In a prospective trial comparing topotecan and paclitaxel, single-agent paclitaxel has been shown to have an ORR of 10% in the third line after platinum and topotecan, and topotecan that of 13% in the third line after platinum and paclitaxel (Gore, 2001). A

retrospective cohort analysis from Israel of patients who were able to receive third-line chemotherapy for metastatic ovarian cancer suggested third-line single-agent response rates of 11.9% (Brucim 2012), while a similar study from Japan showed an ORR of 40.7% (Nishio, 2009).

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

- The endpoint being used for this breakthrough designation request in the current studies is overall response rate (ORR). These trials are continuing to accrue patients, and outcomes will be expressed in terms of ORR.
- Endpoints accepted by the Division in ovarian cancer include ORR, PFS, and overall survival (OS). OS endpoints have become increasingly difficult to assess in trials, as patients undergo multiple subsequent therapies upon completion of a trial; as a result, ORR and PFS are acceptable endpoints for the evaluation of a specific treatment.
- Sporadic genomic losses of heterozygosity (LOH) could putatively be associated with other, non-BRCA-mediated, inefficiency in homologous repair mechanisms; this would be indicative of HRD in the presence of unmutated BRCA, perhaps in the setting of undiscovered mutations in other HRD-associated genes. The Sponsor, Clovis Oncology Inc, has partnered with Foundation Medicine to develop an algorithm for the next-generation sequencing (NGS) analysis of patient tumor genomics in order to define an “HRD score,” which assigns a score based on the number and distribution of genomic LOH “scars” in tumor specimens. The molecular mechanisms for these findings, though not clearly established, should also confer susceptibility to PARP inhibition by rucaparib in tumors bearing these genomic alterations. Preliminary analyses discussed with the sponsor suggest enhanced activity in patients with an elevated HRD score compared to an unmutated population; these studies are ongoing.

4. Brief description of available therapies (if any)

3 rd -Line Regimen	Population	ORR	Reference
Paclitaxel	After platinum, topotecan	10%	Gore et al, JCO, 2001
Topotecan	After platinum, paclitaxel	13%	Gore et al, JCO, 2001
Retrospective analyses:			
Single-agent Paclitaxel, carboplatin,	Retrospective cohort	11.9%	Bruchim et al, Eur J OBGYN Repro Bio, 2012

topotecan, etc.			
Single-agent multiple	Retrospective cohort Disease free interval and PS correlate with response	40.7%	Nishio et al, J Cancer Res Clin Onc, 2009

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

None.

6. Description of preliminary clinical evidence

The Sponsor has aggregated data from two ongoing clinical trials of rucaparib in ovarian cancer to support this breakthrough designation request.

Trial CO-338-010 is a two-part, phase 1/2, open-label, multicenter clinical trial, where part 1 is a phase 1 portion in patients with any solid tumor who have progressed on standard treatment with primary objectives of MTD, RP2D, and safety determination. Part 2 is a phase 2 portion in patients with platinum-sensitive, relapsed ovarian cancer associated with gBRCAm, with primary objective of evaluating ORR by RECIST.

Trial CO-338-017 (ARIEL2) is an open-label, single-arm trial enrolling patients with high-grade serous or grade 2/3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had prior platinum treatment and platinum-sensitive recurrence. On this trial, patients are grouped into one of three groups according to analysis of tumor specimens: tBRCAm (including germline and somatic mutations), non-BRCA HRD, and a biomarker negative population.

In total, 41 patients with BRCAm ovarian cancer whose disease is platinum-sensitive and RECIST-evaluable and who have received > two prior platinum-based treatment regimens, have been enrolled on the two trials and treated with rucaparib 600 mg BID.

In this group, the overall response rate (ORR) has been reported by the sponsor as 66% (27/41), and these RECIST responses have been confirmed in 21 (with five confirmatory scans pending, and one remaining unconfirmed). Seventy-eight percent of the responders (21/27) had continued response at the time of data cutoff, resulting in a duration of response (DOR) that is expected to exceed 25 weeks.

Safety data are available for 163 ovarian cancer patients treated with 600 mg BID rucaparib from the ongoing phase 2 trials. Treatment-related adverse events in > 15% of patients include nausea, vomiting,

diarrhea, abdominal pain, anorexia, anemia, fatigue, and headache, as well as elevations in ALT and AST. The latter have been generally grade 1-2, have an early onset (2-4 weeks of therapy), and are transient or plateau quickly. Delayed myelosuppression is a class effect of the PARP inhibitors and is also seen with rucaparib. Grade 3/4 AEs occurring in >5% of patients include anemia and increased ALT. The toxicity profile of rucaparib monotherapy appears to be less severe than that of combination cytotoxic chemotherapy, and patients have tolerated monotherapy such that management of AEs is accomplished with supportive care and treatment interruption/dose reduction; no patient has discontinued treatment due to a treatment-related adverse event.

7. Division's recommendation and rationale

- Recommendation:
The Division recommends that breakthrough therapy designation for rucaparib as third-line therapy in the treatment of women with BRCAm platinum-sensitive ovarian cancer be granted. The sponsor has met the two key requirements (Section 902, FDASIA) for Breakthrough Therapy Designation: The condition is serious, and life threatening; the sponsor submitted preliminary clinical evidence indicating that rucaparib may result in clinical improvement over existing therapies.
- Rationale:
 - Comparison of ORR for rucaparib with currently-available regimens is limited by the data available for third-line treatments, which are inconsistent, retrospective, and confounded by selection bias, artificially increasing reported response rates in the studied populations; even in comparison with the best of these results (Nishio, 2009), the ORR seen with rucaparib represents a significant improvement (66% vs. 41%), and is even greater (66% vs. 10-13%) than that in all the other studies. This appears to be a significant breakthrough in efficacy for a third-line treatment in this disease setting. Further, the duration of response of nearly six months at data cutoff appears promising.

Based on available data, treatment with rucaparib appears to be well tolerated, as evidenced by the high treatment adherence rate in the two clinical trials and the absence of treatment discontinuation due to adverse events.

Current third-line treatment options for BRCAm platinum-sensitive ovarian cancer include single-agent cytotoxic chemotherapy and platinum-containing combination cytotoxic chemotherapy; though these patients can continue to receive some benefit from further platinum-based treatment, by the time a patient has completed two courses of platinum, they have been exposed to the cumulative toxicities from agents that tend to have a significant side-effect profile. Inevitably, the patient will develop intolerance or allergy to platinum; a delay in further exposure by treatment with an alternative third-line agent presents an opportunity to postpone or avoid some treatment-related toxicities and optimize quality of life during a platinum-free interval.

Olaparib, another PARP inhibitor, is approved for treatment of women with gBRCAm in the fourth-line setting, regardless of platinum sensitivity, with an ORR of 34%.

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

- The Division has had meetings with the Sponsor for the further development of rucaparib, and has advised the Sponsor regarding development of their ongoing phase 2 and phase 3 clinical trials, and their focus on third-line treatment for women with platinum-sensitive ovarian cancer. The Division has also consulted for CDRH regarding the Sponsor's plans to collaborate with Foundation Medicine for the development of the BRCAm and HRD score assays.

9. References

1. Gore, M., ten Bokkel Huinink, W., Carmichael, J., Gordon, A., Davidson, N., Coleman, R., Spaczynski, M., Héron, J.F., Bolis, G., Malmström, H., et al. (2001). Clinical evidence for topotecan-paclitaxel non--cross-resistance in ovarian cancer. *J. Clin. Oncol.* *19*, 1893–1900.
2. Bruchim, I., Jarchowsky-Dolberg, O., and Fishman, A. (2013). Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. *Eur. J. Obstet. Gynecol. Reprod. Biol.* *166*, 94–98.
3. Nishio, S., Katsumata, N., Matsumoto, K., Tanabe, H., Yonemori, K., Kouno, T., Shimizu, C., Ando, M., Kamura, T., Kasamatsu, T., et al. (2009). Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy. *J. Cancer Res. Clin. Oncol.* *135*, 551–557.

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/s/

SANDRA J BENTON
03/24/2015

AMNA IBRAHIM
03/25/2015



IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Director, Regulatory Affairs
2525 38th Street, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rucaparib (CO-338).

We also refer to the meeting between representatives of your firm and the FDA on November 4, 2014. The purpose of the meeting was to discuss the registration strategy and the clinical study intended to support accelerated approval and Breakthrough Therapy Designation for rucaparib and the acceptability of the proposed GMP starting materials for the commercial formulation of rucaparib.

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, contact Amy Tilley, Regulatory Project Manager at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
Sponsor Slides



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: EOP2

Meeting Date and Time: November 4, 2014
Meeting Location: WO22 Rm 1311

Application Number: IND 106289
Product Name: Rucaparib (CO-338)
Indication: treatment of advanced 14 Page(s) has been ovarian cancer
Sponsor/Applicant Name: Clovis Oncology, Inc. Withh l d i F ll b4

Meeting Chair: Amy McKee, M.D., Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Amna Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Amy McKee, M.D., Clinical Team Leader
Sanjeeve Balasubramaniam, M.D., Clinical Reviewer
Laura Fernandes, Ph.D., Biostatistics Reviewer
Abraham Tzou, M.D., OMPT/CDRH/OIR/DIHD/IHGB
Nina L Hunter, Ph.D., CDRH Reviewer, OMPT/CDRH/OIR/DMGP/MPCB
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES

Andrew Allen, M.D., Ph.D., Chief Medical Officer & Executive Vice President
Jeri Beltman, Ph.D., Director, Regulatory Affairs
Heidi Giordano, MA, MBA, Senior Director, Clinical Science
Jeff Isaacson, Ph.D., Senior Director, Biostatistics and Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lindsey Rolfe, MBChB, Vice President, Clinical Development

Foundation Medicine, Inc.

Roman Yelensky, Ph.D., Senior Director, Biomarker & CoDx Development

1.0 BACKGROUND

Rucaparib is currently being evaluated for the treatment of relapsed ovarian cancer in three ongoing clinical studies. Study CO-338-010 (Phase 1/2) and Study CO 338-017 (Phase 2) are single arm open-label studies that include the evaluation of breast cancer gene (BRCA) mutation status as part of the study and analysis plans.

A total of 50 patients with measureable disease and a deleterious BRCA mutation have been enrolled at the recommended dose of 600 mg twice daily in Studies CO 338-010 (Phase 1 [n=4], Phase 2 [n=20]) and CO-338-017 (n=26) to date. The overall population includes patients with platinum-sensitive (n=47) and platinum-resistant (n=3) disease. In study CO-338-010, patients are germline BRCA mutation positive based on local testing, whereas in Study CO 338-017, patients are confirmed as tumor BRCA mutation positive based on central testing.

The majority of the ovarian cancer patients with BRCA mutations (40/50, 80%) remain on rucaparib treatment. The preliminary RECIST overall response rate in these patients is 27/47 (57%) and the combined RECIST/CA 125 overall response rate is 33/47 (70%), according to the sponsor. Patients with platinum-sensitive disease had a RECIST response rate of 59% (26/44), whereas patients with platinum-resistant disease had a RECIST response rate of 33% (1/3).

Response data are also available from eight patients with BRCA mutations and platinum-resistant disease treated in Study CO 338-010 Part 1 at doses ≥ 360 mg. The RECIST overall response rate (ORR) was 2/8 (25%).

Clovis proposes to further characterize the efficacy signal in platinum-resistant, relapsed, tBRCA+ ovarian cancer patients. Specifically, Clovis proposes to amend Study CO-338-010 to add a Part 3 that will enroll approximately 100 patients with platinum-resistant, relapsed ovarian cancer and a deleterious BRCA mutation. The population will include patients with ovarian cancer whose disease relapsed within 6 months after the completion of platinum-based regimen and who may or may not have received additional lines of treatment in the platinum-resistant setting; patients whose disease did not respond or progressed while on platinum-based therapy (platinum-refractory) will not be eligible. Patients will be enrolled based on the BRCA test result in their medical record, and their tumor BRCA (tBRCA) status will be confirmed based on tumor tissue analysis using a central laboratory test. The central laboratory test will be performed by Foundation Medicine, Inc (FMI) and use the BRCA mutation classification algorithm previously discussed with FDA.

Since rucaparib treatment in this molecularly-defined group of patients with platinum-resistant ovarian cancer and a tBRCA mutation is likely to provide a meaningful clinical advantage over existing therapies, the sponsor suggests that a single-arm study with the primary endpoint of response rate as defined by RECIST, with key secondary endpoints including safety and duration of response (DOR), is an appropriate design for accelerated approval.

2. DISCUSSION

Accelerated Approval

Although there are treatments approved for platinum-resistant ovarian cancer, they have limited utility due to poor efficacy (objective response rates ranging 20-30% with median PFS/TTP < 6 months) and significant toxicity. Therefore the development of therapies that offer improved benefit is critically needed.

Rucaparib is currently being evaluated for the treatment of relapsed ovarian cancer in three ongoing clinical studies. Study CO-338-010 (Phase 1/2) and Study CO-338-017 (Phase 2) are single arm open-label studies that include the evaluation of breast cancer gene (BRCA) mutation status as part of the study and analysis plans. Protocol synopses and statistical analysis plans for these studies are provided in Appendix 2 through Appendix 5.

Collectively, a total of 50 patients with measurable disease and a deleterious BRCA mutation (BRCA+) have been enrolled at the recommended dose of 600 mg twice daily (BID) in Studies CO-338-010 (Phase 1 [n=4], Phase 2 [n=20]) and CO-338-017 (n=26) to date. The overall population includes patients with platinum-sensitive (n=47) and platinum-resistant (n=3) disease. In study CO-338-010, patients are germline BRCA+ based on local testing, whereas in Study CO-338-017, patients are confirmed as tumor BRCA+ based on central testing.

The majority of the 50 treated BRCA+ ovarian cancer patients (40/50, 80%) remain on rucaparib treatment. The preliminary response evaluation criteria in solid tumors (RECIST) overall response rate in BRCA+ ovarian cancer patients is 27/47 (57%) and the combined RECIST/CA-125 overall response rate is 33/47 (70%) based on emerging data from the ongoing studies CO-338-010 and CO-338-017 (see Section 4.1, Figure 1 and Section 4.2, Table 1). Of the 19 patients with a partial response (PR) who have had a follow-up scan, 100% have had their PR confirmed. The remaining 8 patients with PRs are between scans and none have yet progressed. Patients with platinum-sensitive disease had a RECIST response rate of 59% (26/44) and a combined RECIST/CA-125 response rate of 70% (31/44). Patients with platinum-resistant disease had a RECIST response rate of 33% (1/3) and a combined RECIST/CA-125 response rate of 66% (2/3).

Response data are also available from 8 BRCA+ platinum-resistant patients treated in Study CO-338-010 Part 1 at doses $\geq$ 360 mg BID (doses believed to be efficacious) in the dose escalation phase of this study (see Section 4.2, Figure 3). The data are mature. The RECIST overall response rate (ORR) was 2/8 (25%) and the combined RECIST/GCIG CA-125 ORR is 4/8 (50%). The median progression-free survival is 9.4 months.

Clovis proposes to further characterize the efficacy signal in platinum-resistant, relapsed, tBRCA+ ovarian cancer patients. Specifically, Clovis proposes to amend Study CO-338-010 to add a Part 3 that will enroll approximately 100 patients with platinum-resistant, relapsed ovarian cancer and a deleterious BRCA mutation. The population will include patients with ovarian cancer whose disease relapsed within 6 months after the completion of platinum-based regimen and who may or may not have received additional lines of treatment in the platinum-resistant

setting; patients whose disease did not respond or progressed while on platinum-based therapy (platinum-refractory) will not be eligible. Patients will be enrolled based on the BRCA test result in their medical record, and their tumor BRCA (tBRCA) status will be confirmed based on tumor tissue analysis using a central laboratory test. The central laboratory test will be performed by Foundation Medicine, Inc (FMI) and utilize the BRCA mutation classification algorithm previously discussed with FDA.

Since rucaparib treatment in this molecularly-defined group of patients with platinum resistant ovarian cancer and a tBRCA mutation is likely to provide a meaningful clinical advantage over existing therapies, a single arm study with the primary endpoint of response rate as defined by RECIST, with key secondary endpoints including safety and duration of response (DOR), is believed to be an appropriate design for accelerated approval.

Question 1

Does the Agency agree that rucaparib treatment of platinum-resistant ovarian cancer in patients with a tBRCA mutation detected by a central laboratory test may be eligible for accelerated approval?

FDA Response:

We do not agree with your proposed regulatory pathway. A treatment IDE is not an option to substitute for an approval/cleared device when that device is called for in the approved drug label. Under the current CoDx policy, if the CoDx (device required for safe and effective use of the drug) is not ready for approval at the time of drug approval, the drug approval will be delayed until such time as the CoDx is approved. A treatment IDE will not suffice for bridging the time between drug and device approval. We expect sponsors to manage their development cycles to minimize delays in device approval, and point to use of the modular PMA pathway to help resolve many issues with the device prior to submission of the drug NDA/BLA.

We recommend that you submit a PMA for the first component, namely the genetic alterations component characterizing tBRCA status, as a CoDx (not as a treatment IDE) to be approved contemporaneously with rucaparib at the time of accelerated approval. The assay will have to be analytically validated in a GMP/QSR laboratory, not a CLIA/central laboratory. If there are any further changes to the device (proposed algorithm refinement and addition of genomic LOH component to the BRCA component), you should submit a second PMA to be approved contemporaneously with rucaparib at the time of full approval.

Sponsor Response to FDA Comment 1:

Clovis appreciates the advice regarding the need for a PMA, and the suggested scenario for PMA submission. Clovis proposes to not discuss this topic further at this upcoming meeting, but intends for this topic to be included in an upcoming CDRH meeting planned for early 2015.

Meeting Discussion:

None

Question 2

Does the Agency agree that a single arm study enrolling approximately 100 patients with relapsed platinum-resistant ovarian cancer and a tBRCA mutation (tBRCA+) that demonstrates meaningful ORR and good tolerability is appropriate and sufficient for accelerated approval in this targeted and underserved population?

FDA Response:

Please refer to Question 1 regarding the need for a PMA for tBRCA mutations at the time of NDA submission.

You may wish to consider examining the ORR in patients who have received three or more lines of chemotherapy regardless of whether their disease is platinum sensitive or platinum resistant.

Sponsor Response to FDA Comment 2:

 (b) (4)
is being considered by Clovis.
We will present a trial design concept for discussion during the meeting.

Meeting Discussion:

The sponsor proposed the following questions:

- **Shall enrollment in ARIEL2a be inclusive of patients who have received ≥ 2 prior chemotherapies, or to those who have received ≥ 3 prior chemotherapies?**

The Agency stated that it would be easier to justify an approval based on ORR in a single-arm study investigating the activity of rucaparib in patients who have received ≥ 3 prior chemotherapy regimens. The Agency also stated that it is difficult to assess what magnitude of ORR would be needed to justify an approval on the basis of ORR in patients who have received ≥ 2 lines of platinum-based chemotherapy.

- **The ARIEL2a study will continue to enroll all patients regardless of BRCA/LOH status. Does FDA agree?**

The Agency agreed.

- **The tBRCA group will include all patients who have a positive central tBRCA test result, including those with a known gBRCA⁺ result, those who are newly diagnosed as gBRCA⁺, and those with sBRCA mutations (new or known).**

The Agency agreed.

- **Clovis anticipates utilizing data from ~100 tBRCA⁺ patients treated at 600 mg BID to support accelerated approval.**
 - **Clovis intends to pool patients in ARIEL2a with existing patients in Study CO-338-010 and/or ARIEL2 to create a dataset of ~100 patients. Does FDA agree?**

The Agency stated that, in general, this approach appears to be reasonable. The final determination of the adequacy of the pooled approach and number of patients will be a review issue.

Confirmatory Study

Study CO-338-014, the ongoing pivotal study in the Clovis rucaparib program, is a double blind, randomized, placebo-controlled Phase 3 study of switch maintenance in platinum sensitive relapsed ovarian cancer patients who are stratified into 1 of 3 molecularly defined subgroups. This study will serve to confirm the efficacy signal observed in Studies CO-338-010 and CO 338-017 (preliminary data shown in see Section 4.1, Figure 1 and Section 4.2, Figure 3), and will also serve to prospectively validate the central laboratory test that will form the basis of a companion diagnostic test. Due to the confirmatory nature of this study, Clovis believes that Study CO 338 014 will be adequate to convert an accelerated approval (based on efficacy and safety in BRCA+ platinum-resistant patients) to the full approval of rucaparib including a FDA approved companion diagnostic (CoDx).

Question 3

Does the Agency agree that Study CO-338-014, a randomized placebo controlled study of switch maintenance treatment in patients with relapsed platinum-sensitive, high-grade ovarian cancer who have achieved a response to platinum-based therapy, is appropriate as a confirmatory study?

FDA Response:

Overall, this development strategy is acceptable. However, as stated previously by the Agency in meetings with you in August and December 2012, whether this trial will support approval will be a review issue and is dependent on the benefit-risk profile of rucaparib. You may wish to consider conducting another study comparing rucaparib versus investigator's choice of chemotherapy in patients with ovarian cancer who have received more than two lines of (b) (4) therapy.

Sponsor Response to FDA Comment 3

Clovis appreciates the confirmation that the CO-338-014 (ARIEL3) is an acceptable development strategy.

(b) (4)

is being considered by Clovis. Clovis does not propose to discuss this topic now, but may request a meeting at a future date should additional discussion be required.

Meeting Discussion:

None

Breakthrough Therapy

Rucaparib is being developed for the treatment of relapsed ovarian cancer, a serious condition. Preliminary safety and efficacy data suggest that rucaparib may be a strong candidate for Breakthrough Therapy Designation.

Although there are approved therapies for the treatment of relapsed ovarian cancer, patients experience significant treatment-related toxicities and eventually succumb to their disease. As such, new therapies with more favorable benefit-risk profiles are needed. Rucaparib, with an alternative mechanism of action as compared with approved therapies whose development includes a molecular patient identification strategy, represents a new therapy with the potential to provide a more favorable benefit-risk profile.

Clovis is conducting two ongoing open label studies in platinum-sensitive relapsed ovarian cancer, CO-338-010 Part 2 and CO-338-017. Thus patients are required to have received at least 2 but no more than 4 prior treatments in Study CO-338-010, or at least one prior platinum-based therapy in Study CO-338-017. Summary data show that the number of prior therapies range from 2 to 4 with a median of 2 prior therapies in Study CO-338-010, and range from 1 to 6, with a median of 1 prior therapy in Study CO-338-017. These observations highlight the fact that women are seeking alternate therapeutic options early in their course of treatment, and emphasizes the need for new and better therapeutic options for the treatment of relapsed ovarian cancer.

Preliminary data from ongoing clinical studies with rucaparib suggest that rucaparib is highly active in patients with ovarian cancer (Table 5). Specifically, RECIST response rates of greater than 50% have been observed in the platinum-sensitive BRCA+ subgroup in each of these two studies. Twenty-six of 43 patients (60%) have had a RECIST response. Of the 19 patients with a PR who have had a follow-up scan, 100% have had their PR confirmed. The remaining 7 patients with PR are between scans and none have yet progressed. The majority of these patients (37/43, 86%) remain on treatment. These results also highlight the importance of identifying specific patient subgroups most likely to respond to rucaparib. The ORR observed in these studies and patient groups are summarized in Table 5.

Patients in Study CO-338-010 are identified as BRCA+ based on a medical record test result, to be confirmed centrally, while patients in Study CO-338-017 are identified as BRCA+ based on a central tumor tissue assay. The ORR in these studies and patient groups suggest that BRCA

mutations are a valid and useful strategy for the identification of patients likely to respond to rucaparib.

In addition to the strong efficacy signal apparent in Table 5, rucaparib has been shown to be well-tolerated. Safety data from the overall rucaparib program was recently evaluated (27 June 2014). This safety report characterized the majority of adverse events as mild to moderate and identified no new significant safety issues. Data are preliminary, yet indicate that rucaparib has a different safety profile than that of standard chemotherapy, an important feature for patients with advanced, symptomatic ovarian cancer who wish to maintain quality of life while continuing to receive treatment for their disease.

Clovis proposes the rucaparib experience in ovarian cancer to date provides an overall profile of efficacy and safety appropriate for breakthrough therapy designation, and that the data summarized in Table 5 may form the basis for a breakthrough therapy designation request.

Question 4

Does the Agency agree that rucaparib administration for ovarian cancer to patients identified as tBRCA+ may be eligible for Breakthrough Therapy Designation?

FDA Response:

Yes. However, we recommend that you carefully define your patient population, as the response rates you cite in your briefing package may not be considered an improvement over available therapy given the survival advantage for platinum doublets in the second-line, platinum-sensitive setting. See also response to Question 2.

Sponsor Response to FDA Comment 4

Based on FDA feedback, Clovis intends to request breakthrough therapy designation for rucaparib. We would like to present the current waterfall plots and discuss the data package appropriate for inclusion in this request in order to reach agreement on the expected content.

Meeting Discussion:

The Agency clarified that a Breakthrough Designation Request (BDR) should include patients who have received at a minimum two prior platinum-based regimens. The sponsor should also include justification based on literature review and approvals in a similar treatment space with a BDR. The Agency advises that a pre-meeting to discuss relevant data for a BDR be requested.

Chemistry, Manufacturing, and Controls

The synthesis of rucaparib camsylate has been consistent through the Phase 2 and Phase 3 clinical studies. The same synthetic route will be utilized for commercial manufacturing. The synthesis utilizes a (b) (4) (b) (4) that has been shown to be robust during scale-up and to provide drug substance of consistently high quality. Clovis proposes to identify the GMP starting

material for rucaparib camsylate synthesis as a (b) (4)
Preparation of the proposed starting material is under the control of Clovis, therefore (b) (4) will be known and consistent. The proposed starting material is well characterized and specifications have been developed which have been shown to result in finished drug substance of appropriate quality. (b) (4)

(b) (4) The proposed starting material also provides significant structural components to the finished drug substance. Therefore, based on the definition of GMP starting materials defined in ICH Q7, Clovis proposes identification of the (b) (4) as the GMP starting material.

Question 5

Does the Agency agree that the (b) (4) is acceptable as the GMP starting material for synthesis of rucaparib camsylate?

FDA Response:

(b) (4) is not an acceptable starting material for the manufacture of rucaparib camsylate because (b) (4) (b) (4)

Also, in your NDA submission include the following information for the proposed starting materials:

- a. Impurity profiles
- b. In-house acceptance criteria and vendor's COA
- c. Brief description of synthetic strategies and methods of manufacture
- d. Detailed discussion on carry-forward impurities
- e. Controls and analytical methods to separate and measure appropriate impurities.
- f. Supplier information for the starting materials used to manufacture
- g. Detailed discussion on (b) (4) studies using impurities to demonstrate the ability of the manufacturing process (b) (4)
- h. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.

Sponsor Response to FDA Comment 5

Clovis appreciates the clear response from FDA and will take under advisement the recommendations regarding designation of GMP starting materials for the drug substance

synthesis, and recommendations for additional information required in the NDA submission. Clovis proposes to not discuss this topic at the upcoming meeting.

Meeting Discussion:

None

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical

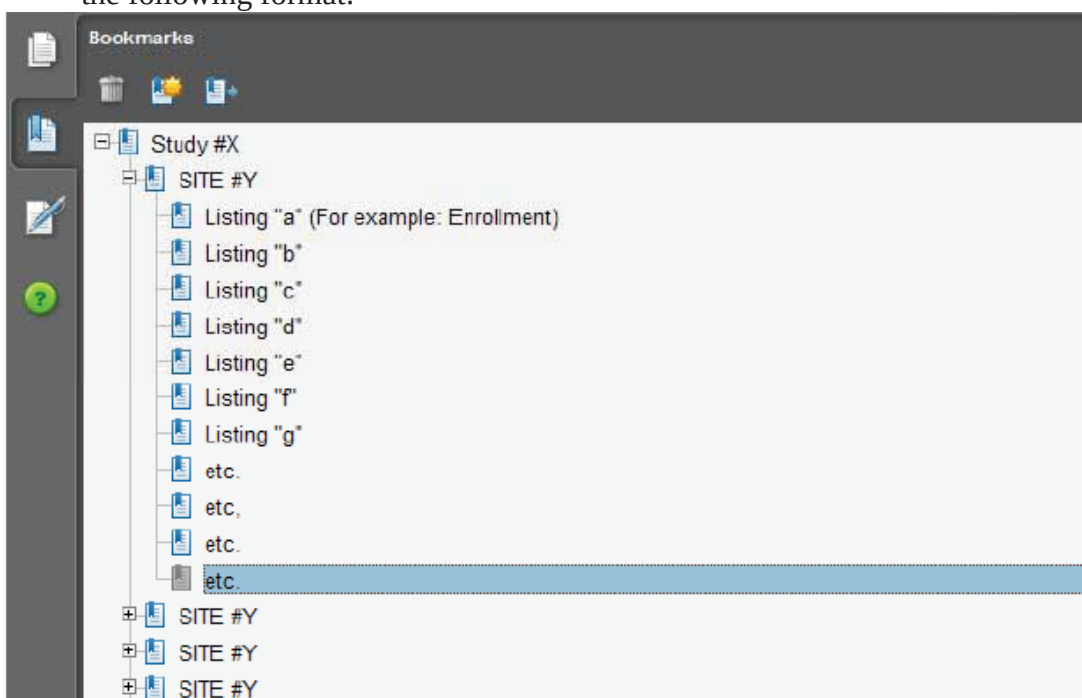
investigator's participation in the study, we request that this updated information also be provided.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

- f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



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

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

References:

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

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slides

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/s/

AMY E MCKEE

11/05/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
Director, Regulatory Affairs
2525 28th Street, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rucaparib (CO-338).

We also refer to the meeting between representatives of your firm and the FDA on May 6, 2014. The purpose of the meeting was to present an updated clinical development plan and gain agreement on the methodology and analyses to be applied to the clinical data from the pivotal Phase 3 clinical study for rucaparib, in support of approval and labeling.

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, contact Amy Tilley, Regulatory Project Manager at (301) 796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Meeting Minutes
Sponsor Slides



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: May 6, 2014
Meeting Location: WO22 Rm 1419

Application Number: IND 106289
Product Name: Rucaparib (CO-338)
Indication: Rucaparib is being investigated for the treatment of patients with ovarian cancer associated with (b) (4), as defined by the presence of a deleterious *BRCA* mutation in tumor tissue (b) (4).
(b) (4)

Sponsor/Applicant Name: Clovis Oncology, Inc.

Meeting Chair: Amy McKee, M.D., Clinical Team Leader
Meeting Recorder: Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Amna Ibrahim, M.D., Acting Director, DOP1
Geoffrey Kim, M.D., Acting Deputy Director, DOP1
Amy McKee, M.D., Clinical Team Leader
Gwynn Ison, M.D., Clinical Reviewer
Shenghui Tang, Ph.D., Biostatistics Team Leader
Stella Karuri, Ph.D., Biostatistics Reviewer
Danuta E Gromek-Woods, Ph.D., Chemistry Reviewer, ONDQA
Reena Philip, PhD, Deputy Director, DIHD/OIVD/CDRH/FDA
Abraham Tzou, M.D., OMPT/CDRH/OIR/DIHD/IHGB
Elizabeth Mansfield, Ph.D, Director, Personalized Medicine Staff, OIVD/CDRH/FDA
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES

Andrew Allen, M.D., Ph.D., Chief Medical Officer & Executive Vice President
Jeri Beltman, Ph.D., Director, Regulatory Affairs
Heidi Giordano, MA, MBA, Senior Director, Clinical Science
Jeff Isaacson, Ph.D., Senior Director, Biostatistics and Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President, Technical Operations

Roman Yelensky, Ph.D., Director, Clinical Genomic Analysis, Foundation Medicine, Inc.

1.0 BACKGROUND

Rucaparib, Clovis' poly (ADP-ribose) polymerase (PARP) inhibitor, is currently in Phase 2 and Phase 3 clinical trials. Identification of appropriate patients for rucaparib therapy is a key element of the development strategy. Clovis and Foundation Medicine (FMI) are collaborating on the development of a companion diagnostic (CDx) for use by physicians to identify patients most likely to respond to rucaparib treatment. This CDx is being developed in parallel with the clinical development of rucaparib.

Through a series of experiments and data analyses, Clovis and FMI have determined the optimal method for identifying tumors with non-BRCA mediated HRD is to assess genomic scarring by quantifying the percentage of loss of heterozygosity across the tumor genome (tumor genomic LOH). The assay uses a single pre-specified algorithm (Analysis Algorithm 1) to combine the identification of deleterious mutations in tumor BRCA1 and BRCA2 with tumor genomic LOH to assess overall HRD status.

Study CO-338-017 is a Phase 2, multicenter, open-label study that will evaluate the efficacy and safety of rucaparib as treatment for relapsed, platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer. Archival and screening tumor samples will be collected from all patients and analyzed by NGS. The primary objective of this study is to evaluate the efficacy of rucaparib in molecularly-defined HRD subgroups using a pre-defined algorithm (Analysis Algorithm 1). This analysis will in turn inform the analysis, using Analysis Algorithm 2, of Study CO-338-014.

Study CO-338-014 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that will evaluate the efficacy and safety of rucaparib as switch maintenance therapy following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer. Archival tumor samples will be collected from all patients and analyzed by NGS. The primary objective of this study is to evaluate the efficacy of rucaparib versus placebo as measured by the primary endpoint, PFS by RECIST, in molecularly-defined HRD subgroups using a pre-specified algorithm (Analysis Algorithm 2) based on the results of CO-338-017. This study will be conducted in parallel with Study CO-338-017, but completed later. In Study CO-338-014, the initial CTA (ICTA) will be utilized to stratify patients for randomization at study entry into 1 of 3 HRD subgroups (BRCA, nbHRD, and biomarker negative) based on deleterious mutations observed in 30 genes. The ICTA examines 30 genes involved in HRR, including the BRCA1, BRCA2, and 28 other HRR genes. The primary analysis is the comparison of PFS between rucaparib and placebo in molecularly defined subgroups, based on a final CTA (FCTA) using Analysis Algorithm 2. The subgroup of patients classified as tBRCA at randomization will be the same subgroup classified as tBRCA for the first step in the step-down procedure for the final analysis. The second step in the step-down procedure for final analysis will be based on the final HRD approach established at the end of Study CO-338-017 and thus may not exactly match the nbHRD subgroup used for stratifying the randomization. There should be considerable overlap between the nbHRD classifications used for randomization and final analysis so there is a high probability that the treatment groups will be balanced within the nbHRD subgroup defined for

the final analysis. The FCTA will be utilized to categorize the HRD status of patients prior to completion of Study CO-338-014. Thus, the primary efficacy analysis will be based on Analysis Algorithm 2, a prospectively defined HRD algorithm.

Clinical validation and outcome data from Study CO-338-014 will form the basis for concurrent NDA and PMA submissions.

2.0 DISCUSSION

Question 1:

Study CO-338-017 is an open-label single arm Phase 2 study in which patients are classified as homologous recombination deficient (HRD⁺ or HRD⁻) based on a genomic scarring approach, CTA. The primary objective of Study CO-338-017 is to determine the efficacy of rucaparib in HRD subgroups defined by the CTA. Another purpose of Study CO-338-017 is to help optimize the algorithm and numerical cut-off that separates HRD⁺ from HRD⁻. Outcome data from Study CO-338-017 will be analyzed using a pre-specified algorithm (Analysis Algorithm 1). Study CO-338-017 is being conducted in parallel with Study CO-338-014, a blinded randomized Phase 3 study. The algorithm and cut-off for Study CO-338-014 will be based on results of Study CO-338-017 and denoted as Analysis Algorithm 2. The LOH cut-off to be used in analysis algorithm 2 has not yet been specified. However, Analysis Algorithm 2 (including the LOH cut-off) will be defined prior to Study CO-338-014 blind break and database lock (DB lock), so that the HRD subgroups in Study CO-338-014 are prospectively defined prior to the analysis of any unblinded Study CO-338-014 data, as depicted in **Error! Reference source not found.**

Does the FDA agree that the (b) (4) in Study CO-338-014?

FDA Response:

No, we do not agree. (b) (4)

(b) (4)

Meeting Discussion:

The FDA clarified that the HRD subgroup will be a prospectively defined sub-group in study 14. FDA recommends that this identification occur as early as possible in the trial. However, there is a potential for imbalances in prognostic factors for each arm. The sponsor acknowledges this risk and addressed its efforts to control for these factors. FDA also recommended that the sponsor address potential variability in single-agent platinum versus platinum doublet regimens by investigators prior to rucaparib therapy. FDA recommends that the eligible patients be those who have received a platinum doublet.

Question 2:

The proposed statistical efficacy analysis for Study CO-338-014 is a nested approach that will evaluate the efficacy of rucaparib (as measured by progression-free survival [PFS]) versus placebo among three subgroups of patients in an ordered step-down fashion. The patient groups for the purpose of statistical analysis, depicted in **Error! Reference source not found.** and defined in **Error! Reference source not found.**, include:

- tBRCA⁺ (positive for a tumor BRCA deleterious mutation)
- HRD⁺ (inclusive of tBRCA⁺/LOH⁺; tBRCA⁺/LOH⁻; tBRCA⁻/LOH⁺)
- intent-to-treat population (ITT), inclusive of all randomized patients

The efficacy of rucaparib versus placebo will first be evaluated in the tBRCA⁺ subgroup of patients. If the efficacy of rucaparib is statistically superior in the tBRCA⁺ subgroup, the efficacy of rucaparib versus placebo will then be tested in the HRD⁺ subgroup of patients. If the efficacy of rucaparib versus placebo in the HRD⁺ subgroup is again statistically superior, the efficacy of rucaparib versus placebo will then be determined in the ITT group. All testing will be performed using a 1-sided significance level of 0.025. If a test does not meet this level, then the results of that test and all subsequent tests will not be considered statistically significant. Sensitivity analyses will also be performed to confirm that the positive benefit shown in the HRD⁺ group is not being driven solely by the tBRCA⁺ subgroup.

Does FDA agree that a nested step-down analysis is a valid approach that may be used to support labeling statements regarding the tBRCA subset, (b) (4)

FDA Response:

(b) (4)

Meeting Discussion:

The sponsor requested feedback regarding the proposed removal of the IRR PFS in the step-down analysis plan and clarified that the IRR assessment still will occur. FDA stated this is acceptable. The sponsor requested clarification as to what extent it would be required to assess gBRCAm and described a novel exploratory approach using tumor biopsies and deep sequencing. FDA stated that the Agency would like to see the patients' historical known BRCA status in the case report forms for the trial. CDRH reiterated its lack of knowledge regarding performance of the various assays for BCRA status that may comprise the historical records.

Question 3:

The NGS-HRD CTA is a single test, utilizing a single algorithm applied to a single tumor DNA sequence data file. One tumor DNA sequence data file is generated per patient sample. The algorithm analyzes the tumor sequence data file to identify sequence variants in the BRCA1 and BRCA2 genes and to compute the percentage of the genome with LOH through analysis of single nucleotide polymorphism (SNP) sequence data. An overview of this method and algorithm is provided in Section **Error! Reference source not found.**. The output from this algorithm will be a single report that describes multiple elements including tBRCA status, tumor genomic LOH status, and the overall HRD classification.

The NGS-HRD CTA will be applied to the pivotal study final analysis to classify patients into groups for sequential efficacy testing per the nested step-down analysis described in Section **Error! Reference source not found.** and **Error! Reference source not found.**. Based on the prospective clinical validation of the NGS-HRD CTA in the pivotal study, CO-338-014, this CTA will be submitted as a PMA for approval as a companion diagnostic (CDx) test.

Does FDA agree the NGS-HRD CTA that includes tBRCA (positive/negative) status, tumor genomic LOH (positive/negative) status, and overall HRD classification (positive/negative) constitutes a single test applicable to a single PMA?

FDA Response:

The currently proposed NGS-HRD CTA appears to be a single test suitable for a PMA submission. Further discussion with CDRH is warranted when detailed device information and validation plans are submitted to CDRH for review.

Meeting Discussion:

None

Question 4:

The tumor suppressor genes, BRCA1 and BRCA2, were discovered as major genes linked to familial breast and ovarian cancer. These discoveries prompted the health care community to

pursue a genetic test that would identify women and family members potentially at risk for developing BRCA-associated cancers. These risk-based tests evaluate germline BRCA (gBRCA) mutations in blood, but do not evaluate somatic BRCA (sBRCA) mutations, which are common in HGSOc, or other tumor characteristics. The importance of evaluating tumor characteristics beyond gBRCA mutations is highlighted by the fact that only approximately 15% of patients have a hereditary form of the disease, while the majority of ovarian cancer cases are sporadic.

In order to appropriately characterize patients who may be responsive to rucaparib, Clovis has chosen to take an alternative approach that goes beyond the identification of patients with gBRCA mutations. (b) (4)



a. Does FDA agree that it is important to specify the use of a tumor-based BRCA test that captures both germline and somatic BRCA mutations within the tumor itself in describing the patient population for whom rucaparib is indicated?

FDA Response:

Product labeling is a review issue and will be addressed at the time of any future NDA submission.

Meeting Discussion:

None



FDA Response:

No, see response to Question 4a.

Meeting Discussion:

None

3.0 OTHER IMPORTANT MEETING LANGUAGE

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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

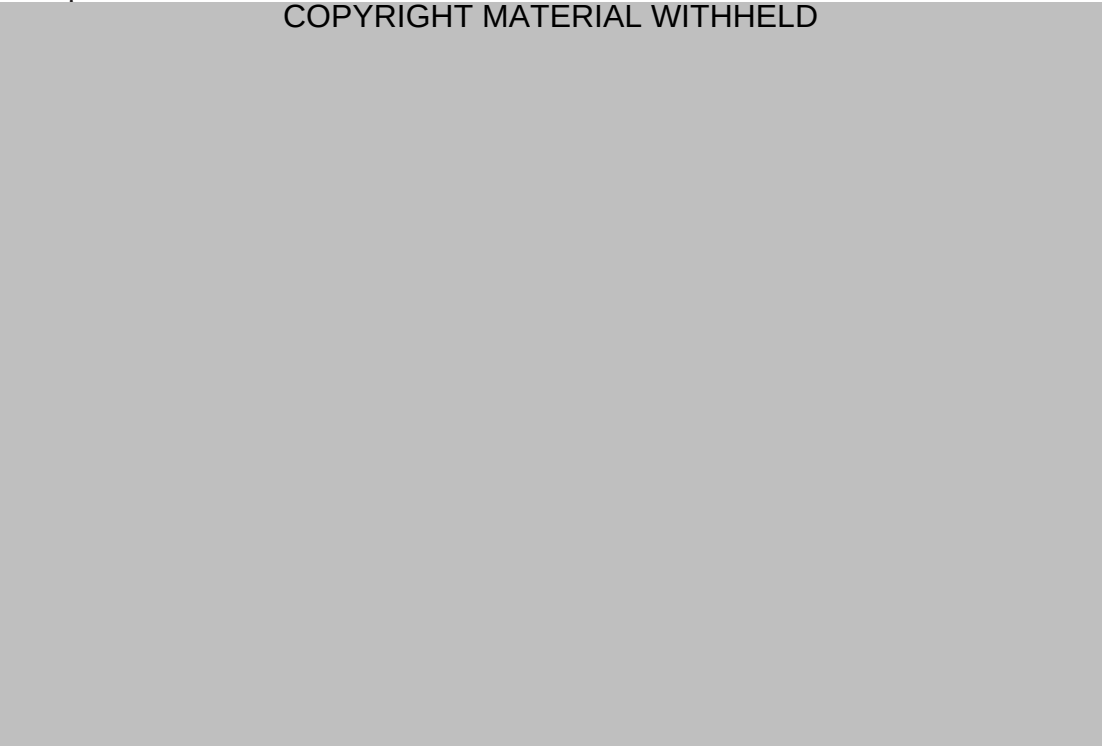
5.0 ACTION ITEMS

None

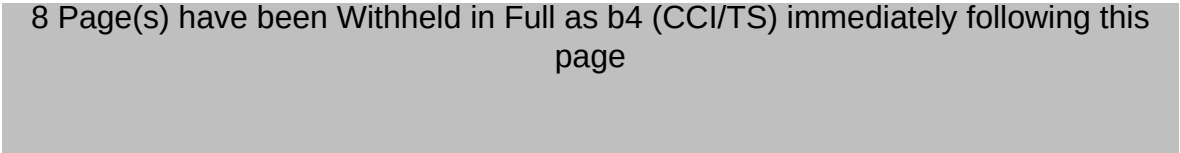
6.0 ATTACHMENTS AND HANDOUTS

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/s/

AMY E MCKEE

05/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Director, Regulatory Affairs
2525 28th Street, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rucaparib (CO-388).

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2012. The purpose of the meeting was to discuss methodology and analysis to collect patient reported outcome (PRO) data in the upcoming pivotal clinical study for rucaparib.

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 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

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: December 14, 2012 3:00 PM- 4:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Silver Spring, MD 20903

Application Number: IND 106289
Product Name: Rucaparib (CO-388)
Indication: Treatment of advanced (b) (4) tumors
Sponsor/Applicant Name: Clovis Oncology, Inc.

Meeting Chair: Amy McKee, MD, Clinical Team Leader, DOP1
Meeting Recorder: Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, DOP1

FDA ATTENDEES

Robert Justice, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Amy McKee, MD, Clinical Team Leader, DOP1
Geoffrey Kim, MD, Medical Officer, DOP1
James Stansbury, Consumer Safety Officer, OMPT
Shengui Tang, PhD, Statistics Team Leader, DOP1
Stella Karuri, PhD, Statistical Reviewer, DOP1
Todd Palmby, PhD, Acting Pharm/Tox Supervisor, DHOT
Gwynn Ison, MD, Medical Officer, DOP1
Abraham Tzou, MD, Medical Officer, OIVD, DIHD, CDRH
Alice Kacuba, RN, MSN, RAC, CPMS, DOP1
Rajesh Venugopal, MPH, MBA, RPM, DOP1

SPONSOR ATTENDEES

Andrew Allen, MD, PhD, Chief Medical Officer & Executive Vice President
Jeri Beltman, PhD, Director, Regulatory Affairs
Heidi Giordano, MA, MBA., Director, Clinical Science
Jeff Isaacson, PhD, Director, Biostatistics and Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President, Technical Operations

(b) (4)

Meeting Minutes
Type C**BACKGROUND**

Clovis is developing rucaparib, a small molecule poly-adenosine diphosphate ribose polymerase (PARP) inhibitor, for ovarian cancer. Rucaparib is currently in Phase 1/2 clinical studies, and future studies leading to approval are planned. To that end, FDA and Clovis held a Type C meeting on 03 August 2012 to discuss the overall rucaparib development strategy of treating a molecularly targeted subset of patients with ovarian cancer. Subsequent to that meeting, the development strategy has been revised based on FDA's feedback, and is outlined in the background package submitted on November 13, 2012 by Clovis. The changes included in the synopsis are summarized in Table 1.

Table 1. High-level Summary of Changes to Study CO-338-014

Design Aspect	Previous	Current
Overall Design	Randomized, Double-Blind, Placebo-Controlled Switch Maintenance Study in Platinum-Sensitive, High-Grade Ovarian Cancer (OC)	Randomized, Double-Blind, Placebo-Controlled Switch Maintenance Study in Platinum-Sensitive, Relapsed High-Grade Serous Ovarian Cancer (HGSOC)
Study population	<i>gBRCA</i> , platinum-sensitive relapsed OC patients who achieved an objective response (partial response [PR] or complete response [CR]) by RECIST to platinum based chemotherapy	Platinum-sensitive HGSOC patients who achieved an objective response (PR or CR) by RECIST, or by GCIG CA-125 criteria to platinum based chemotherapy
Patient identification	Local <i>gBRCA</i> testing to identify biomarker-positive patients	Central testing of tumor tissue to identify biomarker-positive (<i>BRCA</i> HRD or non- <i>BRCA</i> HRD) and biomarker-negative patients
Randomization stratification factors	1. <i>BRCA1</i> vs. <i>BRCA2</i> 2. Response to last platinum regimen (CR or PR)	3. HRD classification (<i>BRCA</i>, non-<i>BRCA</i> HRD, or biomarker-negative) 4. Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 months or more than 12 months) 5. Best response to last platinum regimen (CR or PR)
Endpoints	• Primary: Progression-free survival, investigator assessed (invPFS) • Secondary: PFS, independent radiology review (irrPFS), safety • Exploratory: Quality of Life (QoL, disease-related symptoms) and overall survival (OS)	• Primary: invPFS • Secondary: irrPFS, QoL, OS, safety and population PK
Design Aspect	Previous	Current
Interim analysis	Safety	Safety
Sample size	125	500

Meeting Minutes
Type C**DISCUSSION****Questions and Response**

1. Does the Agency agree that the proposed [REDACTED] (b) (4)
[REDACTED] is appropriate as a pivotal trial design?

FDA Response:

We reiterate that the clinical benefit of a [REDACTED] (b) (4)

[REDACTED]

You proposed to [REDACTED] (b) (4)
[REDACTED] **In the comments we made in the August 3, 2012 meeting, we strongly recommended that the study be powered to detect a significant difference in OS. We reiterate that you do so and that you perform an interim analysis of OS during analysis of investigator-assessed PFS.**

We encourage you to discuss the development of the investigational and marketed tumor tissue test versions with CDRH. Please address the following issues in your pre-submission: use of central lab results for patient accrual (e.g. biomarker negatives not accrued after limit of 150) compared to unbiased subgroup prevalences, plans for specimen banking, differences between clinical trial assay and market-ready device, as well as the impact of subgroup gene list revision, missing data, and test discordances on blinding, patient stratification, and endpoint evaluation.

Sponsor's Response (December 12, 2012)

- We agree to perform an interim OS analysis at the time of final PFS analysis.
- We anticipate that the interim OS analysis will not show a treatment benefit for the following reasons:
 - BRCA patients are expected to experience the longest survival, regardless of treatment.
 - Rucaparib is expected to have differential effects between the patient subgroups, with patients in the BRCA subgroup experiencing the greatest benefit.

Meeting Minutes
Type C

- Interim OS analyses will be biased because there will be informative censoring, with biomarker-negative patients contributing most early deaths.
- We anticipate that interim OS data is likely to show, at a minimum, that there is no treatment-associated detriment.
- CO-338-014 is powered to detect an OS hazard ratio of 0.6 with 80% power.

Meeting Discussion:

Interim OS is regarded as a safety analysis by the agency, and the powering is acceptable.

2. Does the Agency agree it is appropriate to enroll patients based on an objective response to platinum-based chemotherapy as assessed by either RECIST or GCIG CA-125 criteria?

FDA Response:

This is acceptable but should be done with caution. You may wish to stratify according to whether patients are platinum-sensitive based on RECIST or GCIG CA-125 criteria.

Clovis has selected the

(b) (4)

(b) (4)

(b) (4)

3. Does the Agency agree that the

(b) (4)

instrument is appropriately validated

(b) (4)

FDA Response:

(b) (4)

n of measurement properties has involved a

(b) (4)

Meeting Minutes
Type C

Please clarify what you will measure with the (b) (4)

(b) (4)

•

(b) (4)

Finally, labeling will be a review issue.

Sponsor's Response (December 12, 2012)

(b) (4)

Meeting Discussion:

(b) (4)

Additional FDA Comment:

Please see discussion of endpoints involving symptom assessment in:

DHHS/FDA/CDER and CBER. (2007) Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Meeting Minutes
Type C

Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>

(b) (4)

FDA Response:

The proposed FACIT process for translation and cultural adaptation is adequate as outlined. However, please see our response to Question 3 regarding concerns about content that should be considered before undertaking further efforts in this regard.

(b) (4)

Meeting Discussion:

No discussion took place.

5. Does the Agency agree that the FOSI-18 instrument is appropriate

(b) (4)

(b) (4)

FDA Response:

No.

(b) (4)

(b) (4)

Meeting Minutes
Type C

(b) (4)



Sponsor's Response (December 12, 2012)

(b) (4)



(b) (4)



Meeting Minutes
Type C

(b) (4)

6. Does the Agency agree that these procedures to ensure data quality are adequate, and that the collection frequency and duration are appropriate?

FDA Response:

Collection of symptoms and side effects daily with 24-hour recall, averaged across the week at the intervals you suggest, will provide stronger evidence for those domains.

Sponsor's Response (December 12, 2012)

- Correlation between one-week recall and 24-hour recall is high, 0.7-0.8. ^{a, b, c}
- Daily data collection will substantially increase patient burden.
- Daily data collection will increase the possibility for missing data.
- Given these factors, deviation from the validated recall period of one-week is not merited.
- Recognizing that more frequent data collection may be better, data collection has been revised from once every 12 weeks to once every 4 weeks.

- a. Broderick, J.E., Schneider, S., Stone, A.A., & Schwartz, J.E. Quality of Life Research, 2010, 10.1007/s11136-010-9681-x.
- b. Broderick, J.E., Schwartz, J.E., Vikingstad, G., Pribbernow, M., Grossman, S, Stone, A.A. Pain, 2008, 139, 146-157.
- c. Stone, A.A., Broderick, J.E., Shiffman, S.S., & Schwartz, J.E. Pain, 2004, 107, 61-69.

Meeting Discussion:

(b) (4)

Meeting Minutes
Type C

7. Does the Agency agree that the proposed plan outlined above is adequate for assessing the impact of missing data?

FDA Response:

This approach appears reasonable, but a large amount of missing data will be problematic.

(b) (4)

Meeting Discussion:

No discussion took place.

Approximately 500 patients will be randomized to treatment in this study. A minimum of 150 patients in *BRCA* subgroup, a minimum of 200 patients with non-*BRCA* HRD subgroup, and up to 150 patients in the biomarker-negative subgroup, will be enrolled.

The HRD subgroup (*BRCA* and non-*BRCA* HRD) is large enough to detect a 4 point difference in the mean change from baseline in (b) (4). A total of 150 patients in the *BRCA* HRD subgroup will provide greater than 80% power to detect a 4 point (standard deviation of 8) difference between the 2 treatment groups. Similarly, within the entire HRD subgroup (*BRCA* and non-*BRCA* HRD), a total of 350 patients will provide greater than 90% power to detect a 4 point (standard deviation 10) difference in mean change from baseline between the 2 treatment groups.

A 4 point difference is consistent with meaningful differences that have been established through anchor-based analyses with ECOG Performance scores and with other FACT instruments of similar length.

8. Does the Agency agree that

(b) (4)

FDA Response:

(b) (4)

Meeting Minutes
Type C

Sponsor's Response (December 12, 2012)

- CO-338-014 is a maintenance study.
- Maintenance therapy aims to extend progression-free interval and delay interventions often associated with worsening symptoms and concerns.
- Complete measurement of the benefit of maintenance therapy therefore requires assessment of the impact of interventions upon patients' symptoms and concerns.
- To ensure adequacy of assessment, data collection over 24 months extends past the point of progression for most patients and captures the impact of maintenance therapy

(b) (4)

Meeting Discussion:

(b) (4)

9. Does the Agency agree these are appropriate analysis methods?

FDA Response:

Please see the response to question 4 regarding collecting daily side effects and symptoms and response to question 6 regarding the collection of data for 24 months.

Meeting Discussion:

No discussion took place.

Endpoints for later phase efficacy studies, such as CO-338-014, should evaluate whether the investigational drug provides a clinical benefit. One example of measuring a clinical benefit as described in FDA's guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and

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(b) (4)

10. Does the Agency agree that the (b) (4) adequately assesses a symptom endpoint, indicative of clinical benefit?

FDA Response:

No. Please see the responses to questions 2-4.

Meeting Discussion:

No discussion took place.

(b) (4)

(U) (4)

(U) (4)

(b) (4)

FDA Response:

No. Please see the responses to questions 2-4.

Meeting Discussion:

No discussion took place.

Additional Comments:

1. Please provide justification for the proposed BID dose regimen in trial CO-338-014.

Meeting Discussion:

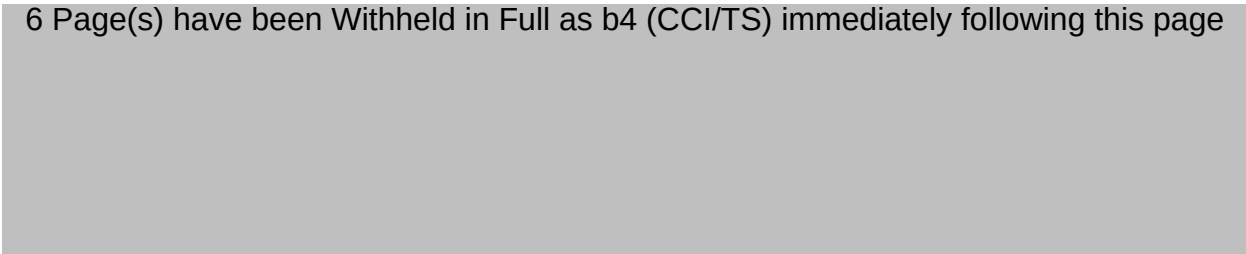
No discussion took place.

Meeting Minutes
Type C

ATTACHMENTS AND HANDOUTS

A copy of the presented slides during the meeting is attached.

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



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/s/

RAJESH VENUGOPAL

01/16/2013

Amended meeting minutes to revise FDA response to question #6. Removed quote taken from Sponsor's background package.

AMY E MCKEE

01/16/2013



IND 106289

MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, Ph.D.
1700 Owens Street, Suite 205
San Francisco, CA 94158

Dear Dr. Beltman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rucaprabib (CO-338).

We also refer to the meeting between representatives of your firm and the FDA on August 3, 2012. The purpose of the meeting was to discuss the development of Clovis' products simultaneously with companion diagnostics, common to all of our development programs.

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 me/ at (301) 796-2103.

Sincerely,

{See appended electronic signature page}

Techiya (Thea) Toaff, R.N., B.S.N.
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance on rucaparib development program strategy.

Meeting Date and Time: August 3, 2012 3:00 pm - 4:00 pm
Meeting Location: FDA WO 22 Room 1311

Application Number: IND 106289
Product Name: CO-338 (formerly PF 01367338), rucaparib
Indication: Treatment of Ovarian Cancer and Breast Cancer in patients with germline BRCA (gBRCA) mutations.
Sponsor/Applicant Name: Clovis Oncology, Inc.

Meeting Chair: Robert L. Justice, M.D., M.S., Director, DOP1
Meeting Recorder: Techiya Toaff, R.N., B.S.N., Regulatory Health Project Manager, DOP1

FDA ATTENDEES

Robert L. Justice, M.D., M.S., Director, DOP1
Geoffrey Kim, M.D., Medical Officer, DOP1
Amy McKee, M.D., Acting Team Leader, DOP1
Antony J. Murgo, M.D., Associate Office Director, OMPT/CDER/OND/OHOP
Laleh Amiri-Kordestani, M.D., Medical Officer, DOP1
Todd Palmby, Ph.D., Supervisory Toxicologist
Haw-Jyh Chiu, Ph.D., Pharm/Tox Reviewer
Shenghui Tang, Ph.D., Biostatistics Team Leader
Robert Becker, M.D., Medical Officer Team Leader, CDRH/OIVD
Abraham Tzou, M.D., Medical Officer, CDRH/OIVD/DIHD
Reena Philip, Ph.D., Supervisory Microbiologist, CDRH/OIVD/DIHD
Maria Chan, Ph.D., Supervisory Microbiologist, CDRH/OIVD/DIHD
Sharon Liang, Ph.D., Reviewer, CDRH/OIVD/DIHD
Rosane Charlab Orbach, Ph.D., Acting Team Leader, Genomics, CDER/OPC
Alice Kacuba, R.N., M.S., RAC, Chief, Project Management Staff, DOP1
Techiya Toaff, R.N., B.S.N., Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES

Andrew Allen, M.D. Ph.D, Chief Medical Officer & Executive Vice President
Jeri Beltman, Ph.D., Director, Regulatory Affairs

Heidi Giordano, M.A., M.B.A., Director, Clinical Science
 Julie Hambleton, M.D., Vice President, Clinical Development
 Jeff Isaacson, Ph.D., Director, Biostatistics and Data Management
 Gillian Ivers-Read, Chief Regulatory Officer and Executive Vice President, Technical Operations
 Mitch Raponi, Ph.D., Senior Director, Molecular Diagnostics

(b) (4)

(b) (4)

BACKGROUND

Platinum-resistant Ovarian Cancer

The Sponsor proposes a single arm study in patients with germline BRCA (BRCA)-associated platinum-resistant ovarian cancer that has progressed after one chemotherapy regimen in the platinum-resistant setting (CO-338-013). Deleterious germline mutations in either *BRCA1* or *BRCA2* are associated with the development of ovarian cancer. While most patients with ovarian cancer, irrespective of their BRCA status, initially respond to platinum-based chemotherapy, resistance to platinum agents develops over time. Once a tumor is platinum-resistant, the patient's overall survival is less than 12 months. Thus patients with platinum-resistant tumors associated with a germline *BRCA* (*gBRCA*) mutation represent a small patient population with significant unmet medical need and limited treatment options.

The proposed single-arm study will evaluate the benefit of rucaparib in patients with BRCA-associated platinum-resistant ovarian cancer who have progressed on one additional non-platinum standard chemotherapy.



Figure 1. Patient Selection for CO-338-013

Specifically, the patient population in the platinum-resistant setting will include women with advanced (Stage III or IV) ovarian cancer who had evidence of radiographic progression or relapse within 6 months after the completion of the last platinum-based regimen as determined by Response Evaluation Criteria In Solid Tumors (RECIST). Patients who progress while on platinum-based therapy (platinum-refractory) will not be eligible. Additionally, a subsequent chemotherapy, such as topotecan, doxil or paclitaxel, must have been administered in the platinum-resistant setting, and progression according to RECIST, either while on or after subsequent therapy will be required. Patients will have documented *gBRCA* mutation as determined according to local practice. All tumor histologies and grades will be eligible.

As this is a single arm study, there is no randomization. A two-stage design will initially enroll 21 patients with a *gBRCA* mutation and platinum-resistant ovarian cancer that progressed on or after standard chemotherapy in the platinum-resistant setting; if 3 of 21 patients have a confirmed objective response, as determined by the investigator, then an additional 29 patients will be enrolled to ensure a total of approximately 50 patients. Rucaparib will be administered on a daily basis until disease progression.

The primary endpoint is overall response rate (ORR) as determined by independent radiologic review (IRR). Key secondary and exploratory endpoints include duration of response (DOR) as determined by IRR; ORR and DOR as determined by the investigator, safety and overall survival (OS). Due to the unmet medical need of this patient population, the Sponsor deems this study appropriate for consideration of accelerated approval.

DISCUSSION

Questions and Responses

1. In this small, unmet medical need population of patients with *gBRCA* mutation and platinum-resistant ovarian cancer that has progressed on a therapy administered in the platinum-resistant setting, the Sponsor believes a single arm study with an ORR as the primary endpoint is appropriate and will be sufficient for consideration for accelerated approval.

Does the Agency agree that this trial design appropriately identifies a patient population with high unmet medical need, and that the trial design and the ORR primary endpoint are appropriate and sufficient for consideration of accelerated approval?

FDA Response:

No. There is undoubtedly variability in the quality of data generated by local laboratories and it will be necessary to have an approved test for deleterious BRCA 1 and 2 mutations at the time of proposed approval of rucaparib. We recommend that you use, in CO-338-013 and CO-338-014, the test that will be marketed. Alternatively, your proposed studies should include a clinical validation plan for your in vitro diagnostic test; you must show that the performance characteristics of the assay that will be marketed are comparable to those of the assay used in your clinical studies. It is not clear that Clovis has a companion diagnostic co-development plan in place.

CDRH does not have sufficient information regarding BRCA testing laboratories to comment on whether different testing algorithms and processes as well as classification methods of deleterious BRCA1/2 germline mutations would be sufficiently defined, consistent, validated and controlled for appropriate use in identifying patients for rucaparib therapy.

We are concerned that your patient population may not be representative of the population of ovarian cancer patients who have BRCA mutations (i.e., the population for which rucaparib will be indicated). Eligibility for BRCA testing based on clinical criteria identifies only a subset of mutation carriers. You should save blood samples from all enrolled subjects and from a representative group of non-enrolled patients, to compare results from the test(s) used to enroll subjects with results from the test that will be marketed. The exact indication for the marketed test will be a review issue.

You should also address the potential prognostic implications of BRCA 1 versus BRCA 2 mutations in terms of better chemosensitivity and longer overall survival being reported in some series of patients with BRCA 2 mutations compared to BRCA 1 mutations and wt BRCA 1/2.

The response rate should be of sufficient magnitude to “provide meaningful therapeutic benefit to patients over existing treatments” and a confirmatory study should be underway at the time of approval (21 CFR 314 Subpart H). Also, the proposed sample size of the single-arm study is too small to support an accelerated approval. You have not provided justification as to why a randomized trial versus an “available therapy” cannot be conducted in this disease setting using endpoints that directly measure clinical benefit. We recommend an additional meeting once you have preliminary phase II data.

In addition, in your proposed confirmatory clinical trial, it is unclear whether a prolongation of PFS in the maintenance setting of platinum sensitive disease represents direct clinical benefit to the patient, and the trial is not powered to detect a difference in overall survival. Whether this trial would support conversion from accelerated approval to full approval will be a review issue and is dependent on the magnitude of PFS prolongation and the safety profile of rucaparib. A preferable study design would demonstrate an overall survival improvement in a randomized trial performed in the platinum-resistant setting.

Clovis Response:

Clovis is proposing a staged approach to diagnostic co-development. Screening and enrollment will continue to be based on a local lab result. In order to address FDA’s concerns about the variability of the quality of data from local labs, Clovis proposes using a germline BRCA blood test to be conducted at a central laboratory for result confirmation. Further diagnostic development, concurrent with the proposed trials, will focus on a tumor tissue-based test that builds on current clinical practice. This new tissue-based somatic BRCA test would then be cross-validated to the existing blood-based central lab test. (b) (4)

The diagnostic development plan will be described at this meeting, and a future discussion with CDRH will be requested.

We acknowledge that the inclusion of only 50 patients in CO-338-013 may not be of sufficient size for approval. Given that this trial is to be conducted in a genetically defined subset of patients where there is unmet need and limited patient availability, what size single-arm trial would FDA consider to be appropriate for accelerated approval? We acknowledge that the risk-benefit profile would be a review issue; however we seek FDA's position on the magnitude of response in a single-arm trial that could be acceptable for accelerated approval.

Meeting Discussion:

Clovis presented their proposed testing procedures for germline BRCA mutations using local laboratory testing. In addition they presented their proposed plan for development of next generation DNA sequencing of tissue for BRCA mutations. Clovis requested feedback regarding to appropriateness of the local laboratory testing, however FDA is not able to make definitive statements regarding this approach. FDA recommends to proceed as quickly as possible to develop their tissue based test.

Historically, we have required at least 100 patients in a rare disease setting to support approval, however the final number needed to support accelerated approval is a review issue.

2. The Sponsor believes the safety data from approximately 50 rucaparib-treated patients with *gBRCA* mutation and platinum-resistant ovarian cancer, supplemented with safety data from an additional monotherapy study using the same dose and schedule (Study CO-338-010; estimated 10 patients with any solid tumor; 41 *gBRCA* ovarian cancer and 41 *gBRCA* metastatic breast cancer [MBC]) will be a sufficiently sized safety database to support accelerated approval. Additional safety data will be provided from completed studies that used the intravenous formulation of rucaparib for short courses (3-5days every 3 weeks) in combination with chemotherapy.

Does the Agency agree that the proposed safety database is sufficient to support an accelerated approval?

FDA Response:

See the response to question 1 regarding the suitability of the sample size of the proposed single-arm study. Note that there is concern regarding the development of secondary malignancies in patients with *gBRCA* mutations that have been previously treated with chemotherapy and are undergoing treatment with PARP inhibitors. Please provide a monitoring plan for the workup of patients with persistent anemia, leukopenia, or thrombocytopenia in your protocols.

Clovis Response:

We do not intend to discuss safety concerns, but acknowledge your concern regarding the development of secondary malignancies. Patients will be followed for secondary malignancies in our trials as they're followed for survival. We would also address this by following OS to show that OS is not decreased in patients exposed to rucaparib.

Meeting Discussion:

No discussion took place at the meeting.

3. The Sponsor believes that the overall design of the proposed switch maintenance clinical study, in particular enrolling patients with a *gBRCA* mutation and platinum-sensitive relapsed ovarian cancer who have achieved a confirmed CR or PR in response to platinum-based therapy and randomizing them to maintenance rucaparib vs. placebo until disease progression, is an appropriate design for ovarian cancer.

Does the Agency agree that the proposed design for a switch maintenance study is appropriate in the platinum-sensitive relapse ovarian cancer setting?

FDA Response:

See response to Question 4.

Meeting Discussion:

No discussion took place at the meeting.

4. The Sponsor believes prolongation of PFS as a primary endpoint of the magnitude expected in this trial and with its associated delay in subsequent chemotherapy and attributed toxicities, is an adequate and appropriate measure of clinical benefit and is sufficient for approval in this targeted patient population. The Sponsor believes this study is adequately powered to observe a meaningful PFS difference supported by a positive benefit-risk profile.

Does the Agency agree that PFS as a primary endpoint and the associated secondary endpoints, if satisfied in this targeted patient population, represent clinical benefit sufficient to warrant regulatory approval?

FDA Response:

Please see response to question 1 regarding the suitability of using laboratory developed tests for patient selection and the suitability of the PFS endpoint to support conversion of accelerated approval to regular approval. The evaluation of PFS in ovarian cancer can be problematic due to the difficulties in radiographic measurements of the disease. While this concern is somewhat mitigated by the proposed inclusion of patients with evaluable disease only and the use of RECIST 1.1 to define progression, the clinical benefit of a PFS improvement in the maintenance setting has not been validated. As stated in the response to question 1, whether this trial will support approval will be a review issue that is dependent on the benefit-risk profile of rucaparib. You should power this trial for OS with sufficient number of deaths to detect a pre-specified median difference in OS.

Clovis Response:

We acknowledge FDA's concerns regarding the collection of progression data in ovarian cancer setting. Specific criteria for assessing progression and site training to assure consistent practices will be employed to address these concerns. Investigator assessed PFS is the primary endpoint. In addition an independent radiologic review will be conducted on all patients will be included as a secondary endpoint. PFS can be used as a surrogate for OS and we will be assessing OS as a secondary endpoint, or PFS may be used as a surrogate for QoL as outlined in the background briefing materials. We acknowledge that the magnitude of effect and risk-benefit will be a review issue. We wish to discuss the FDA's view on the use of the QoL endpoint in conjunction with a PFS endpoint in the context of full approval.

Meeting Discussion:

FDA recommend that if a QoL end point is to be included in the labeling that a separate meeting need to be requested.

5. BRCA testing has been widely available for greater than 15 years, is recommended for all patients diagnosed with high grade serous ovarian cancer by NCCN guidelines, and is used by patients and physicians to make major medical decisions. As such BRCA testing is part of standard medical care and the patient's medical record. Therefore, the Sponsor will identify patients with a *gBRCA* mutation based on documentation in the patient's pre-existing medical record. The Sponsor believes that BRCA testing performed according to local practice, by a laboratory that has received an international or country-specific quality standards certification, will appropriately identify the target population for the two proposed clinical studies.

Does the Agency agree that the proposed patient identification strategy is:

- a) Appropriate for patient selection for enrollment in Studies CO-338-013 and CO-338-014
- b) Sufficient to support approval and therapeutic product labeling?

FDA Response:

No. See response to question 1.

Meeting Discussion:

No discussion took place at the meeting.

Question 6:

The sponsor believes the proposed extended toxicology program is sufficient to support initiation of the proposed clinical program in ovarian cancer.

Does the Agency agree that data from the 1-month repeat-dose toxicity studies in dog and rat, consequent characterization of the target organ toxicities, and supplemental human safety data is adequate support for the initiation of the proposed clinical study?

FDA Response:

Yes. In addition, given the completed nonclinical toxicology studies and the current human safety data, the results of the proposed 1-month repeat-dose toxicity study in rats may not be needed prior to initiating the proposed Phase 2 clinical trial.

Clovis Response:

No discussion required.

Meeting Discussion:

No discussion took place at the meeting.

7. Does the Agency agree that pending the results of an initial non-GLP dose range finding developmental toxicity study in the rat, additional confirmatory studies may not be warranted?

FDA Response:

Yes. However, the adequacy of the proposed non-GLP dose-range finding embryo-fetal developmental toxicology study in rats or the need for additional embryo-fetal developmental toxicology studies to support a NDA for rucaparib can only be determined following review of the final study report submitted to the IND.

Clovis Response:

No discussion required.

Meeting Discussion:

No discussion took place at the meeting.

8. Rucaparib (b) (4) range from (b) (4) nm through about (b) (4) nm. In addition, localization to pigmented tissues, including hair/fur and eye, was noted in rats (Section 4.1.3). Thus, an in vivo phototoxicity study using pigmented Long-Evans rats will be

conducted. Preliminary in-life results will be available to inform the proposed clinical trials, while final results (including histology) will be available by end 2012.

Does the Agency agree that conducting an in vivo phototoxicity study concurrent with the initiation of the proposed clinical trials is appropriate?

FDA Response:

Yes.

Clovis Response:

No discussion required.

Meeting Discussion:

No discussion took place at the meeting.

9. Rucaparib was evaluated in an in vitro cytogenetic assay using human lymphocytes. Clastogenic activity was noted following 3 hours of incubation with and without metabolic activation (Report 02-2371-01, submitted in IND Serial No. 0000). This response in mitotically-stimulated cells was anticipated based on the mechanism of action of rucaparib (PARP inhibition and DNA repair).² For this reason, no in vivo micronucleus test is proposed for the development of rucaparib.

FDA Response:

Yes. Based on the positive findings of rucaparib genotoxicity in *in vitro* studies, FDA agrees that additional *in vivo* genotoxicity studies are not warranted to support a NDA in the proposed patient population.

Clovis Response:

No discussion required.

Meeting Discussion:

No discussion took place at the meeting.

Additional Comments:

- 1. Your protocols (CO-338-013 and CO-338-014) should describe how your drug will be administered with regard to food.**
- 2. We recommend that you plan to collect PK data using sparse sampling in your pivotal efficacy trials protocols (CO-338-013 and CO-338-014). This would be important in evaluating exposure-response relationships for your drug for measures of both, effectiveness and toxicity. Refer to the Guidance for Industry entitled “*Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*” found at**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

3. Evaluate food effect on the bioavailability of the study drug. Food-effect bioavailability information should be available to guide dosing recommendations with regard to food intake for the clinical efficacy and safety trials. Conduct a food effect trial per Guidance for Industry entitled “*Food-Effect Bioavailability and Fed Bioequivalence Studies*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf>.
4. Determine bioavailability of the study drug in humans per Guidance for Industry entitled “*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>.
5. If the study drug has pH dependant solubility, determine the potential for a drug- drug interaction with drugs (such as proton pump inhibitors, histamine receptor antagonists, antacids) that alter the gastric pH.
6. If the study drug will be developed in combination with other drugs, evaluate the potential for a PK interaction between the study drug and the other drugs in the combination therapy during the development of this combination therapy.
7. There are reports of secondary somatic mutations of BRCA 1 and 2 that may confer drug resistance. We encourage you to examine pre-treatment and post-progression tumor biopsies for such mutations to further understand the mechanisms of sensitivity and resistance to PARP inhibitors.
8. Rucaparib is metabolized by genetically polymorphic enzymes. Poor metabolizers may be at greater risk of toxicity. FDA recommends that you collect germline DNA from all patients in rucaparib clinical trials at baseline to allow for pharmacogenetic analyses in case outliers are identified.

Clovis Response:

Clovis intends to address these points during clinical protocol development.
No discussion required at this time.

Meeting Discussion:

No discussion took place at the meeting.

ATTACHMENTS AND HANDOUTS PROVIDED BY THE SPONSOR DURING THE MEETING

Figure: Bridging strategy of gBRCA LDT to tissue BRCA companion diagnostic



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/s/

TECHIYA TOAFF

08/10/2012

Corrected IND Number from 106283 to 106289 on meeting minutes letterhead

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209115

LATE-CYCLE MEETING MINUTES

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) dated June 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rubraca™ (rucaparib) 200 mg and 300 mg tablet.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 10, 2016.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 10, 2016; 1:00pm – 2:00pm EST

Meeting Location: WO Bldg. #22, Conf. Room 4201

Application Number: NDA #209115

Product Name: Rubraca™ (rucaparib)

Applicant Name: Clovis Oncology, Inc.

Meeting Chair: Julia Beaver, MD

Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
Sara Horton, MD, Clinical Reviewer, DOP1
Todd Palmby, PhD., Non Clinical Team Leader, DHOT
Jinzhong Liu, PhD, Clinical Pharmacology Reviewer, DCP5
Qi Liu, PhD, Clinical Pharmacology Team Leader, DCP5
Rosane Charlab-Orbach, PhD, Genomics Team Leader, OCP
Laura Fernandes, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Xiao-Hong Chen, PhD, Pharmaceutical Assessment Lead, OPQ
Hisani Madison, PhD, CDRH Reviewer, DMGP
Capt. William Pierce, PharmD, Associate Director for Labeling, DOP1
Rowe Medina, PharmD, Reviewer, DMPP
Kim J. Robertson, Regulatory Health Project Manager, DOP1

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

APPLICANT ATTENDEES

Jeri Beltman, PhD, Senior Director, Regulatory Affairs
Hanna Cho, PhD, Manager, Regulatory Affairs
Jeff Etter, PhD, Vice President, Pharmaceutical Development
Heidi Giordano, MA, MBA, Vice President, Clinical Science
Sandra Goble, MS, Associate Director, Biostatistics
Jeff Isaacson, PhD, Vice President, Biostatistics & Data Management
Gillian Ivers-Read, Chief Regulatory Officer & Executive Vice President
Lara Maloney, Director, Clinical Science
Lindsey Rolfe, MBChB, Chief Medical Officer & Executive Vice President

Andrew Simmons, PhD, Senior Director, Translational Medicine
Jim Xiao, PhD, Associate Director, Clinical & Nonclinical Pharmacology

1.0 BACKGROUND

NDA 209115 was submitted on June 23, 2016 for Rubraca™ (rucaparib) 200 mg and 300 mg tablet.

Proposed indication(s): monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.

PDUFA goal date: February 23, 2017

FDA issued a Background Package in preparation for this meeting on November 8, 2016.

2.0 DISCUSSION

1. Introductory Comments (Kim J. Robertson/Julia Beaver, MD)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Each issue will be introduced by FDA and followed by a discussion:

- Clinical PMR: Submit the results of ARIEL 3 and ARIEL 4 (update on status)
- Clinical PMC: Germline BRCA test
- Clinical Pharmacology PMR: Hepatic impairment study (Moderate); (b) (4) drug-drug interaction study

Clinical Pharmacology: Status of the Mass Balance Study; characterization of metabolites

Discussion:

- Discussed the PMRs and PMC; the sponsor and The Agency are in agreement.
- Fifteen out of fifteen patients have been enrolled on the drug-drug interaction study.
- The metabolite study is anticipated to complete enrollment by Q3 2017.

3. Discussion of Minor Review Issues

- Labeling Concerns from the Applicant

- (b) (4)

Discussion:

- Clovis found the revisions to Section 14 acceptable.
- The Agency asked Clovis to propose alternative language for the QTc section.
- The Agency asked Clovis to propose alternative language for the laboratory abnormality description of AST/ALT text.
- The Agency notified Clovis that it would slightly modify the indication statement regarding the companion diagnostic and send them proposed language by November 10, 2016. The applicant in turn was to provide return labeling with all recommendations by November 15, 2016.

4. Additional Applicant Data

Discussion: No discussions necessary.

5. Information Requests

Discussion: Clovis stated they would provide partial CMC Information Request information on November 10, 2016 and additional information the week of November 14, 2016.

6. Discussion of Upcoming Advisory Committee Meeting

Discussion: Clovis was notified that an Advisory Committee Meeting was not planned.

7. REMS or Other Risk Management Actions

Discussion: Clovis was informed that a REMS is not necessary.

8. Postmarketing Requirements/Postmarketing Commitments

Discussion: Clovis was notified that the PMRs/PMCs were forthcoming.

9. Major Labeling Issues

Discussion: No discussion was necessary.

10. Review Plans

Discussion: Clovis was informed that the review of their application was still underway and we would continue submitting information requests if necessary during the review process. Clovis was also informed to submit its promotional materials to be used after the 120 days following marketing approval (i.e., its post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement, should the application be approved.

11. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

JULIA A BEAVER
11/30/2016

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, November 08, 2016 6:43 PM
To: 'Jeri Beltman'
Subject: RE: Clovis LCM
Attachments: Final Late-Cycle Meeting Background Package NDA 209115 Rubraca (rucaparib) (COR-MEET-07).pdf

Importance: High

Hi Jeri:

Please see the background information we have prepared for the Late Cycle Meeting slated for Thursday, November 10, 2016. Please note that the team has been apprised of the topics of possible interest to Clovis for the teleconference meeting. Perhaps this document may answer some questions for Clovis.

Some of Clovis' questions may be best answered during the t-con; other questions you asked (i.e., Is it possible to know are the individual discipline reviews complete, or what is the schedule? Is there a schedule for the primary review to be completed and a plan for the higher level reviews?) are not providing guidance per se, but are more our internal specifics/milestones that we generally do not disclose to our sponsors and/or applicants.

It is our intent to provide Clovis with any additional PI comments by tomorrow, November 9, 2016. If we have any substantive matters to discuss at this juncture, I assure you that the concerned disciplines will mention them at the time of the meeting and if need be, as the review process continues.

The MCM minutes will be forthcoming very soon.

Please see the following call-in information re: the LCM:

Teleconference information

- 1. Dial: Local: (b) (4)
Toll free: (b) (4)
2. Follow the instructions that you hear on the phone.
MeetingPlace Meeting ID: (b) (4)

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Food and Drug Administration
Division of Oncology Products 1
Ofc. Phone: (301) 796-1441
Fax: (301) 796-9845
Email: kim.robertson@fda.hhs.gov

From: Jeri Beltman [<mailto:jbeltman@clovisoncology.com>]
Sent: Tuesday, November 08, 2016 11:00 AM
To: Robertson, Kim
Subject: Clovis LCM

Dear Kim-

Based on our phone call yesterday, I am left with the impression that FDA may not consider that there sufficient topics to warrant a F2F meeting, or that the timing is not quite right for the topics that merit discussion. We are looking to FDA for guidance regarding the F2F versus teleconference option as well as the timing for the meeting itself.

We are looking to you for guidance because we do not know what outstanding or critical review issues remain. At the time of the MCM meeting no significant review issues were raised. Although Clovis does not expect a formal MCM communication until 30 days after the meeting (i.e., Nov. 20th), we have no information regarding the contents of this communication to guide us. As such, we would like to point out that currently we do not know where we stand in the review process and this is why F2F discussion or formal teleconference would be useful.

For instance, Clovis is seeking clarity regarding several topics for which we understand information should be available at this point in the review. We further understand that although it is not possible to communicate the official action until the review is complete, some guidance to the sponsor could be provided concerning the following:

- Is it possible to know are the individual discipline reviews complete, or what is the schedule?
- Have the inspection reports been received and are there any issues?
- When can we expect the next round of PI comments?
- Is there a schedule for the primary review to be completed and a plan for the higher level reviews?

In addition to the specific agenda questions provided yesterday, Clovis hopes you find the above bulleted comments appropriate for inclusion at the late cycle meeting.

I look forward to your feedback as early as possible today. In particular, if FDA is still considering a teleconference in lieu of a F2F meeting, then the Clovis team will need time to alter our travel plans. I will give you a call to discuss the LMC plans (F2F vs teleconference, as well as the agenda) at 9:00 am PST / 12:00 (noon) EST.

Regards, Jeri

Jeri Beltman, Ph.D.
Sr. Director, Regulatory Affairs
Clovis Oncology, Inc.
Phone: (415) 409-5465
jbeltman@clovisoncology.com
www.clovisoncology.com



NDA 209115

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Clovis Oncology, Inc.
Attention: Jeri Beltman, PhD
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
Boulder, CO 80301

Dear Dr. Beltman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rubraca (rucaparib), 200 mg and 300 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 10, 2016.
Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 10, 2016; 1:00pm-2:00pm, EST
Meeting Location: WO Bldg. #22; Conf. Room 4201 (teleconference)

Application Number: NDA # 209115
Product Name: Rubraca® (rucaparib)
Indication: Ovarian Cancer
Sponsor/Applicant Name: Clovis, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), 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.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, 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:
Clinical PMRs and PMCs
Clinical Pharmacology studies

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Kim J. Robertson/Julia Beaver, MD)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion:

- Clinical PMR: Submit the results of ARIEL 3 and ARIEL 4 (update on status)
- Clinical PMC: Germline BRCA test
- Clinical Pharmacology PMR: Hepatic impairment study (Moderate); (b) (4) drug-drug interaction study
- Clinical Pharmacology: Status of the Mass Balance Study; characterization of metabolites

3. Discussion of Minor Review Issues – 10 minutes

- Labeling Concerns from the Applicant
- (b) (4)

4. Review Plans – 5 minutes

The Division anticipates it will continue its expedited review of the application, barring no unexpected shift in work priorities or team staffing. If unexpected significant issues arise during the course of the review, the review plan will default to normal priority review timelines.

5. Wrap-up and Action Items – 5 minutes (TBD following LCM)

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/s/

GEOFFREY S KIM
11/08/2016

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/s/

KIM J ROBERTSON
11/10/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209115

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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Attention: Jeri Beltman, PhD
Senior Director, Regulatory Affairs
5500 Flatiron Parkway, Suite 100
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{See appended electronic signature page}

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

ENCLOSURE:
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Indication: Ovarian Cancer
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ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

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/s/

GEOFFREY S KIM
11/08/2016