CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209936Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **209936** SUPPL # HFD # **161**

Trade Name **ALIQOPA™**

Generic Name **copanlisib**

Applicant Name **Bayer HealthCare Pharmaceuticals, Inc.**

Approval Date, If Known **September 14, 2017**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5-year (new chemical entity)
7-year (orphan drug exclusivity)

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Rosa J. Lee-Alonzo, PharmD
Title: Regulatory Project Manager
Date: September 13, 2017

Name of Division Director signing form: Albert Deisseroth, MD, PhD
Title: Supervisory Associate Division Director

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

/s/

ROSA J LEE-ALONZO
09/14/2017

ALBERT B DEISSEROTH
09/14/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **209936** BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **ALIQOPA** Established/Proper Name: **copanlisib** Dosage Form: **injection**		Applicant: **Bayer HealthCare Pharmaceuticals Inc.** Agent for Applicant (if applicable):
RPM: Rosa Lee-Alonzo, PharmD		Division: Division of Hematology Products

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

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

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

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

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

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action: • User Fee Goal Date is 11/16/2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval; 9/14/2017
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
• Original applicant-proposed labeling	☒ Included
❖ 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
• Original applicant-proposed labeling	☒ Included
❖ 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
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	Letter: 6/1/2017 Review: 5/31/2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 5/25/2017 DMEPA: 8/8/2017; 7/18/2017 DMPP/PLT: 8/18/2017 OPDP: 8/13/2017 SEALD: ☒ None CSS: ☒ None Product Quality: 8/10/2017 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/16/2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ 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 *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

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

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan designation	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	9/13/2017, 9/12/2017 (2), 9/9/2017, 9/7/2017, 9/1/2017 (2), 8/25/2017 (2), 8/21/2017, 8/16/2017, 8/9/2017 (2), 8/7/2017, 7/28/2017, 7/26/2017, 7/25/2017, 7/18/2017, 7/17/2017, 7/13/2017, 7/11/2017, 6/30/2017, 6/28/2017, 6/26/2017, 6/21/2017, 6/15/2017, 6/6/2017, 6/2/2017 (2), 6/1/2017 (2), 5/24/2017, 5/23/2017, 5/22/2017, 5/15/2017, 5/4/2017, 5/2/2017, 4/19/2017, 3/30/2017, 3/21/2017, 12/30/2016
❖ 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)	Clinical Memorandum: 9/13/2017
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	10/18/2017
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	7/7/2017
• Late-cycle Meeting *(indicate date of mtg)*	8/15/2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 18
Division Director Summary Review *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 17
Cross-Discipline Team Leader Review *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 1
PMR/PMC Development Templates *(indicate total number)*	6 PMRs

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 2, 3, 4, and 7
• Clinical review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 2, 3, 4, 7, 8, and 9
• 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)*	Page 144 of 9/13/2017 Multidisciplinary Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ 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)*	DRISK Review: 7/28/2017
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	8/10/2017
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)*	See 9/13/2017 Multidisciplinary Review Section 16
Statistical Team Leader Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 7
Statistical Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 7
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 15
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 6
Clinical Pharmacology review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 6 IRT/QT Review: 9/8/2017
❖ 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)*	See 9/13/2017 Multidisciplinary Review Section 14
• Supervisory Review(s) *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 5
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	See 9/13/2017 Multidisciplinary Review Section 5
❖ 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
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Integrated Quality Assessment 8/10/2017 Executive Summary 8/9/2017 Drug Substance 7/24/2017 Drug Product 7/21/2017 Labeling 8/10/2017 Process 7/25/2017 Facilities 8/3/2017 Microbiology 7/20/2017 Method Validation 7/25/2017
❖ 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)*	Page 7 of Integrated Quality Assessment
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	8/3/2017 ☒ Acceptable ☐ 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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	☒ Done

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

/s/

ROSA J LEE-ALONZO
09/15/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Wednesday, September 13, 2017 2:28 PM
To: 'Anita Murthy'
Subject: RE: NDA 209936 ALIQOPA_PMR #6_Response due ASAP

Hi Anita,

The modification is acceptable.

Rosa

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Wednesday, September 13, 2017 1:57 PM
To: Lee-Alonzo, Rosa
Subject: RE: NDA 209936 ALIQOPA_PMR #6_Response due ASAP

Dear Rosa – we noticed a small omission in PMR-3, please see the track change and clean version. Please let me know if the Division agrees.

Regards,

Anita

From: Lee-Alonzo, Rosa [mailto:Rosa.Lee-Alonzo@fda.hhs.gov]
Sent: Wednesday, September 13, 2017 12:04 PM
To: Anita Murthy
Subject: RE: NDA 209936 ALIQOPA_PMR #6_Response due ASAP
Importance: High

Hello Anita.

The PMRs are considered agreed upon. Please submit the final PMR worksheet officially by today.

Thank you.

Rosa

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Tuesday, September 12, 2017 11:28 AM
To: Lee-Alonzo, Rosa
Subject: RE: NDA 209936 ALIQOPA_PMR #6_Response due ASAP
Importance: High

Dear Rosa – reference is made to NDA 209936 and to the Division's revisions to the PMRs received 12 September. Attached please find Bayer's response. Note, as discussed earlier today, Bayer has requested an additional modification to PMR-2 which is detailed in the response.

Regards,

Anita

From: Lee-Alonzo, Rosa [mailto:Rosa.Lee-Alonzo@fda.hhs.gov]
Sent: Tuesday, September 12, 2017 9:25 AM
To: Anita Murthy
Subject: NDA 209936 ALIQOPA_PMR #6_Response due ASAP

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

Review the FDA revised PMRs with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

We request a response to the PMRs **ASAP**.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

The information contained in this e-mail is for the exclusive use of the intended recipient(s) and may be confidential, proprietary, and/or legally privileged. Inadvertent disclosure of this message does not constitute a waiver of any privilege. If you receive this message in error, please do not directly or indirectly use, print, copy, forward, or disclose any part of this message. Please also delete this e-mail and all copies and notify the sender. Thank you.

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/s/

ROSA J LEE-ALONZO
09/13/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, September 12, 2017 12:05 PM
To: 'Anita Murthy'
Subject: NDA 209936 -- FDA Labeling Revisions Response Due 4:30 PM TODAY
Attachments: NDA 209936 Aliqopa_FPI_To Bayer_DHP_12Sep2017.docx

Dear Anita,

Please see the attached FDA labeling revisions to the full prescribing information (FPI) for NDA 209936 Aliqopa

Review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, send the revised tracked changes labeling documents (PI) to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

Please submit your response to the labeling (FPI) revisions by **4:30 PM Today.**

Kindly confirm receipt of this correspondence and contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
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/s/

ROSA J LEE-ALONZO
09/12/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, September 12, 2017 9:25 AM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMR #6_Response due ASAP
Attachments: NDA 209936 Aliqopa - PMR #6 to Bayer_DHP_12Sep2017.docx

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

Review the FDA revised PMRs with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

We request a response to the PMRs **ASAP**.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
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Division of Hematology Products
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/s/

ROSA J LEE-ALONZO
09/12/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Saturday, September 09, 2017 9:03 PM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMR #6_Response due Sept 12, 9:00 AM

Importance: High

Dear Anita,

Please refer to your submission dated March 16, 2017 for NDA 209936 Aliqopa and review the Post Marketing Requirement (PMR #6) below:

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later.

PMR-6 (FDAAA PMR)

Complete and submit results of a study to determine the effect of Aliqopa on the QT interval.

PMR/PMC Schedule Milestones:	Enrollment Completed:	MM/YYYY
	Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

We request a response to the PMR no later than Tuesday, **September 12, 2017, 9:00 AM EST.**

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
09/09/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Thursday, September 07, 2017 11:47 AM
To: 'Anita Murthy'
Subject: NDA 209936 -- FDA Labeling Revisions Response Due Sept 11, 11 AM EST
Attachments: NDA 209936 Aliqopa_FPI_To Bayer_DHP_7Sep2017.docx

Dear Anita,

Please see the attached FDA labeling revisions to the full prescribing information (FPI) for NDA 209936 Aliqopa

Review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, send the revised tracked changes labeling documents (PI) to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

Please submit your response to the labeling (FPI) revisions by Monday, **September 11, 2017, 11:00 AM.**

Kindly confirm receipt of this correspondence and contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
09/07/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, May 23, 2017 2:26 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_QT studies review
Attachments: Highlights_ClinPharm_and_Cardiac_Safety.doc

Good afternoon, Anita.

Could you please send a completed "Highlights ClinPharm and Cardiac Safety" form (attached) by **Tuesday, May 30, 2017 12:00 PM EST**?

Also, I will be sending you the official filing letter by the end of this week.

Please let me know if you have any questions.

Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
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Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

ROSA J LEE-ALONZO
09/06/2017

From: Lee-Alonzo, Rosa
To: "Anita Murthy"
Subject: NDA 209936 -- FDA Labeling Revisions Response Due Sept 6, 12 PM EST
Date: Friday, September 01, 2017 2:21:00 PM
Attachments: image001.png
ALIQOPA (copanlisib) NDA 209936_FPI_To Bayer_DHP_1Sep2017.docx
ALIQOPA (copanlisib) NDA 209936_PPI_To Bayer_DHP_1Sep2017.docx

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Dear Anita,

Please see the attached FDA labeling revisions to the full prescribing information (FPI) and Patient Package Insert (PPI) for NDA 209936 Aliqopa.

Review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, send the revised tracked changes labeling documents (PI) to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

Please submit your response to the labeling (FPI, PPI) revisions by Wednesday, **September 6, 2017, 12:00 PM.**

Kindly confirm receipt of this correspondence and contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
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/s/

ROSA J LEE-ALONZO
09/01/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, September 01, 2017 2:10 PM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMRs_Response due Sept 6, 12:00 PM
Attachments: NDA 209936 Aliqopa - PMRs to Bayer_DHP_1Sep2017.docx

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

Review the FDA revised PMRs with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

We request a response to the PMRs no later than Wednesday, **September 6, 2017, 12:00 PM EST**.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
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Division of Hematology Products
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/s/

ROSA J LEE-ALONZO
09/01/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, August 25, 2017 3:53 PM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMRs_Response due Aug 30, 1:00 PM
Attachments: 6 NDA 209936 Aliqopa - PMRs to Bayer_DHP_ 25Aug2017.docx

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

Review the FDA revised PMRs with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

We request a response to the PMRs no later than Wednesday, **August 30, 2017, 1:00 PM EST**.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
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/s/

ROSA J LEE-ALONZO
08/25/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, August 25, 2017 4:12 PM
To: 'Anita Murthy'
Subject: NDA 209936 -- FDA Labeling Revisions Response Due Aug 30, 1PM EST
Attachments: ALIQOPA (copanlisib) NDA 209936_FPI_To Bayer_DHP_25Aug2017.docx; ALIQOPA (copanlisib) NDA 209936_PPI_To Bayer_DHP_25Aug2017.docx

Dear Anita,

Please see the attached FDA labeling revisions to the full prescribing information (FPI) and Patient Package Insert (PPI) for NDA 209936 Aliqopa.

Review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, send the revised tracked changes labeling documents (PI) to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

Please submit your response to the labeling (FPI, PPI) revisions by Wednesday, **August 30, 2017, 1:00 PM.**

Kindly confirm receipt of this correspondence and contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

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

ROSA J LEE-ALONZO
08/25/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Monday, August 21, 2017 10:22 AM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMRs_Response due Aug 24, 1:00 PM
Attachments: NDA 209936 Aliqopa - PMRs to Bayer_DHP 21Aug2017 (2).docx

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

Review the FDA revised PMRs with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

We request a response to the PMRs no later than Thursday, **August 24, 2017, 1:00 PM EST**.

Also, we were not able to anonymize our revisions because Bayer's revisions were anonymized. Please do not anonymize your revisions.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
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rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
08/21/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Wednesday, August 16, 2017 10:22 AM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA response to Bayer's dose adjustment proposal with strong CYP3A inhibitors

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa. We also refer to Bayer's new proposal related to dose adjustment with strong CYP3A inhibitors received via email on August 13, 2017.

FDA Response:
The recommendation of reducing ALIQOPA dose to 45 mg when given concomitantly with strong CYP3A inhibitors is mainly due to the safety concern related to the 53% AUC increase when ALIQOPA is coadministered with strong CYP3A inhibitors such as itraconazole. We note that the maximum tolerated dose (MTD) of copanlisib was determined to be 0.8 mg/kg, which is equivalent to the proposed dose of 60 mg. Therefore, coadministration of ALIQOPA with strong CYP3A inhibitors will increase patients exposure to copanlisib above MTD exposures.

For the purpose of dosing recommendation, inter-study exposure comparisons maybe problematic due to potential differences in study population. Therefore, slight dose reduction to 45 mg QD is safe and reasonable approach for patients who need concomitant strong CYP3A inhibitors.

Please let me know if you have any questions.

Thank you.

Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
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rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
08/16/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Wednesday, August 09, 2017 12:42 PM
To: 'Anita Murthy'
Subject: NDA 209936 ALIQOPA_PMRs_Response due Aug 16, 1:00 PM
Attachments: NDA 209936 Aliqopa - PMRs.docx

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa and review the Post Marketing Requirements (PMRs) in the attached document.

We request a response to the PMRs no later than Wednesday, **August 16, 2017, 1:00 PM EST**.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by teleconference if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially, the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times.

Final PMR designation numbers will be assigned later.

PMR-1 (Accelerated Approval PMR)

(b) (4)

PMR/PMC Schedule Milestones:	Enrollment Completed:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMR-2 (FDAAA PMR)

(b) (4)

PMR/PMC Schedule Milestones:	Enrollment Completed:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMR-3 (FDAAA PMR)

Characterize the long-term safety of Aliqopa (copanlisib) as monotherapy and in combination with immunochemotherapy, along with safety-related concomitant medication use, in patients (b) (4) Submit annual interim (b) (4) datasets from a prospective cohort of at least 400 patients (b) (4) at least 5 (b) (4)

PMR/PMC Schedule Milestones:		
	Enrollment Completed:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Interim Report Submission (Year 1):	MM/YYYY
	Interim Report Submission (Year 2):	MM/YYYY
	Interim Report Submission (Year 3):	MM/YYYY
	Interim Report Submission (Year 4):	MM/YYYY
	Final Report Submission (Year 5):	MM/YYYY

PMR-4 Hepatic Impairment

Amend and complete your ongoing clinical pharmacokinetic trial (Study 18041) to determine an appropriate safe dose of Aliqopa (copanlisib) in patients with moderate and severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMR-5 Renal Impairment

(b) (4)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC-6 Drug-Drug Interactions (DDI) - perpetrator drug as inhibitors of transporter MATE2-K

Conduct a clinical pharmacokinetic (PK) trial to evaluate the effect of ALIQOPA (copanlisib) on the pharmacokinetics of metformin (a sensitive MATE2-K substrate) to address the potential for PK and pharmacodynamic (such as serum lactate) interaction. This trial should be designed and

conducted in accordance with the FDA Guidance for Industry entitled, "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*"

PMR/PMC Schedule Milestones:	Draft Protocol Submission	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

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/s/

ROSA J LEE-ALONZO
08/09/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Monday, August 07, 2017 8:37 PM
To: 'Anita Murthy'
Subject: NDA 209936 -- FDA Labeling Revisions Response Due Aug 17, 1PM EST
Attachments: NDA 209936 Aliqopa_to Bayer_7Aug2017.docx

Dear Anita,

Please see the attached FDA labeling revisions to the prescribing information (PI) for NDA 209936 Aliqopa.

Review the FDA revised labeling with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)

After you have made any necessary changes, send the revised tracked changes labeling documents (PI) to me via email before you make your official submission electronically to the NDA file. **Any edits you make should be in tracked changes.**

Please submit your response to the labeling (PI) revisions by Thursday, **August 17, 2017, 1:00 PM.**

Kindly confirm receipt of this correspondence and contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
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/s/

ROSA J LEE-ALONZO
08/07/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, July 28, 2017 8:00 AM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due Aug 1, 1:00 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than Tuesday, **August 1, 2017, 1:00 PM EST**.

Clinical Information Request
FDA review of hypersensitivity reactions in patients treated with copanlisib revealed that all cases at least possibly-related to copanlisib exhibit cutaneous manifestations only and it is unclear if the reactions were truly hypersensitivity reactions. Please provide a summary of patients treated with copanlisib that developed anaphylaxis or required acute anti-histamine therapy or systemic corticosteroids.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/28/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Wednesday, July 26, 2017 2:46 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due August 2. 12:00 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

The revisions to the container labels are acceptable. However, we request a response to the following additional carton information request no later than Wednesday, **August 2, 2017, 12:00 PM EST**.

Carton Information Request

A. Carton Labels

1. We recommend increasing the prominence of the strength presentation of 60 mg*in the primary display panel (PDP) per 21 CFR 201.15(a)(6). As currently presented, the font size is too small and can be easily overlooked. Please consider reducing the graphics on the label to allow more space for increasing the font size.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/28/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, July 25, 2017 1:07 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due Aug 1, 1:00 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than Tuesday, **August 1, 2017, 1:00 PM EST.**

Clinical Information Request
Please provide the following information:

1) Provide an analysis and integrated dataset of the interventions required in patients with **treatment emergent adverse event of hypertension** in the indolent NHL population (Pool 1) and the NHL/CLL population (Pool 2). The Agency plans to further characterizes the pre-dose hypertension events and post-dose hypertension events. See table below (one row per copanlisib dosing visit) for some of the information to be included.

Pre-dose Hypertension

USUBID	Preferred Term	Toxicity Grade	Visit	Assessment Date	Pre-dose Blood Pressure	Pre-dose BP ≥ 150/90	Anti-HTN Med required	Anti-HTN Medication	Copanlisib dose given
						Yes or No	Yes or No		Yes or No[1]

[1] If No, provide the duration of the dose delay

Post-dose Hypertension

USUBID	Preferred Term	Toxicity Grade	Visit	Assessment Date	Post-dose BP required intervention	Post-dose BP	Anti-HTN Med required	Anti-HTN Medication
					Yes or No		Yes or No	

2) Provide a summary of patients with indolent NHL (Pool 1) and NHL/CLL (Pool2) with the **treatment emergent adverse event of hypertension** that required initiation or an additional chronic anti-hypertension medication during treatment with copanlisib.

3) Please provide an analysis and integrated dataset of the interventions required in patients with **treatment emergent adverse event of hyperglycemia** in the indolent NHL population (Pool 1) and the NHL/CLL population (Pool 2). The Agency plans to further characterizes the pre-dose hyperglycemia events and post-dose hyperglycemia events. See table below (one row per copanlisib dosing visit) for some of the information to be included.

Pre-dose Hyperglycemia

USUBID	Preferred Term	Toxicity Grade	Visit	Assessment Date	Pre-dose Blood Glucose	Pre-dose glucose ≥ 160	Diabetic Med required	Diabetic Medication	Copanlisib dose given

						Yes or No	Yes or No		Yes or No[1]

[1] If No, provide the duration of the dose delay

Post-dose Hyperglycemia

USUBID	Preferred Term	Toxicity Grade	Visit	Assessment Date	Post-dose glucose required intervention	Post-dose blood glucose	Diabetic Med required	Diabetic Medication
					Yes or No		Yes or No	

4) Provide a summary of patients with indolent NHL (Pool 1) and NHL/CLL (Pool2) with the **treatment emergent adverse event of hyperglycemia** that required initiation or an additional chronic diabetic medication during treatment with copanlisib.

5) Provide a summary of patients with indolent NHL (Pool 1) and NHL/CLL (Pool2) with the **treatment emergent adverse event of diarrhea** and **serious adverse event of diarrhea** that required anti-diarrheal medications. Please include summary information on the medications administered.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/25/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, July 18, 2017 3:05 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due July 25 12:00 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than Tuesday, **July 25, 2017, 12:00 PM EST**.

Carton/Container Information Request

A. Container Labels:

1) We recommend relocating and increasing the prominence of the strength of the drug to appear under the drug name in the primary display panel (PDP). As currently presented, the strength of the product is not prominent. In addition, we suggest revising the strength from (b) (4) to read "60 mg*" and include asterisk information separately. Please see below for our suggested revision:

Aliqopa
(copanlisib) for injection
60 mg*
***Equivalent to 69.1 mg copanlisib dihydrochloride**

2) Consider revising the statement (b) (4) to read "Single dose vial – discard unused portion" to minimize the risk of the entire contents of the vial being given as a single dose.
3) Increase prominence of statements "For Intravenous Infusion Only" as currently presented it is difficult to read.
4) The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual container as required per 21 CFR 201.25(c)(2).

B. Carton Labels:

1) See A.1., and A.2.
2) Consider increasing the prominence of the information "Must be reconstituted and diluted" to ensure this important information is not overlooked.
3) The net quantity statement of "One Vial" is not currently present on the principal display panel. Please include the net quantity statement per Draft Guidance: Container and Carton, April 2013 (line 462).

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/18/2017

Lee-Alonzo, Rosa

From: Bouie, Teshara
Sent: Monday, July 17, 2017 11:20 AM
To: anita.murthy@bayer.com
Cc: Lee-Alonzo, Rosa
Subject: NDA 209936 -- Information Request

Hi Anita,

Please amend the table 3- **(Table 3: Stability indicating tests, procedures and acceptance criteria for stability study of the first three production batches)** in the Post approval Stability Commitment with the revised stability specification table.

Please respond by July 21, 2017.

Please confirm receipt of this email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

FDA U.S. FOOD & DRUG ADMINISTRATION

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, July 11, 2017 8:18 AM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due July 17, 2017, 4:30 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than Monday, **July 17, 2017, 4:30 PM EST**.

Nonclinical IR

Please explain discrepancies in the study descriptions for Study No. PH-37826 "Multi Cycle Systemic Toxicity Study in Wistar Rats (Administration via Intravenous Infusion, Three/ Four Treatment Cycles (Females/ Males) Followed by a 8~Weeks Recovery Period)". Specifically, as it is mentioned in Sections 1.2 and 2 of the study report and then in the Toxicology Written and Tabulated Summaries in Module 2 of the submission. In the study report, it states BAY 84-1236 was administered via continuous intravenous infusion at dosages of 0, 0.35, 1.15 and 3.46 mg/kg for 4 dosing cycles to 10 male, and for 3 cycles to 10 female Wistar rats per dose group (=main groups). **A cycle comprised three administrations for 1 hour once a week followed by 2 weeks without administration.** However, in the *Toxicology Tabulated Summary* Page 3, it states Cycles being once a week for 3 weeks + 1 week off, and in Section 7.2 there's a description similar to Section 1.2 of the study report. Further in the *Toxicology Written Summary* Table 1-1, Cycles are described as once a week for 3 weeks + 1 week off and then on Page 12, cycles are described as once a week for 3 weeks followed by 8 week recovery. Please submit a memo clarifying all these descriptions to the NDA in module 2 for review by the Pharm/Tox team.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/14/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Thursday, July 13, 2017 1:49 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due July 31 12:00 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request to be submitted with the other QT information request (sent on June 15, 2017) no later than Monday, **July 31, 2017, 12:00 PM EST**.

QT Information Request

Thank you for adding PR, QRS intervals to the analysis dataset Copanlisib_QTC_data_v3.xpt for Study 18270. However, nominal time points can only be found in Study 16270 Arm B, please include all nominal time points for every observations of all studies unless the observation was not a planned nominal time point by protocol.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

MID-CYCLE COMMUNICATION

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 7, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
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: July 7, 2017; 10:00 – 11:00 AM EDT

Application Number: NDA 209936
Product Name: Aliqopa (copanlisib)
Indication: Patients with relapsed (b) (4) follicular lymphoma (FL) who have received at least two prior therapies
Applicant Name: Bayer HealthCare

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Rosa Lee-Alonzo, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Nicholas Richardson, MD, Clinical Reviewer
Rosa Lee-Alonzo, PharmD, Regulatory Project Manager
Esther Park, PharmD, Regulatory Project Manager
Wanda Nguyen, PharmD, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Pedro Del Valle, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Guoxiang (George) Shen, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPh, Statistical Team Leader
Xin (Cindy) Gao, PhD, Statistical Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Sherita McLamore-Hines, PhD, Acting Quality Assessment Leader

APPLICANT ATTENDEES

Bayer Healthcare, Inc.
Todd Paporello (Regulatory)

Anita Murthy (Regulatory)
Yuchao Xie (Regulatory)
Barry Childs (Clinical Development)
Jose Garcia-Vargas (Clinical Development)
Camille Granvil (Clinical Pharmacology)
Zuzana Jirakova Trnkova (Clinical Pharmacology)
Florian Hiemeyer (Biostatistics)
Ashok Miriyala (Pharmacovigilance)
Hui-Talia Zhang (Pharmacovigilance)
Ursula Uwer (CMC)
Andreas Lender (CMC)
Deborah Flint (CMC)
Melissa Thomas (Project Management)
Olaf Doehr (Non-clinical)
Joachim Grevel (Pharmacometrics)

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

No significant issues were identified.

3.0 INFORMATION REQUESTS

CMC (microbiology) – Due July 12, 2017

1. We acknowledge the information provided in section 3.2.P.7 which states that a 6 mL colorless glass type 1 vial is used for the primary container closure system. Please provide the manufacturer and a product identification number of the 6 mL glass vial proposed for the container closure system of Copanlisib lyophilisate, 60 mg.
2. We acknowledge the information provided in module 3.2.P.2 regarding container closure integrity validation. We note that (b) (4)
3. Please provide a (b) (4) statement for the drug product.

4. We acknowledge the (b) (4) validation information provided in module 3.2.P.3.5 which states that (b) (4) validation study.
5. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 19) regarding the validation of the stopper sterilization process. It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4); however, data supporting these studies were not provided. Please provide data from three recent stopper sterilization runs (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.
6. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 20) regarding the validation of the (b) (4) process. It is stated that (b) (4) the required sterilization criteria and all endotoxin indicators showed a (b) (4) in endotoxins; however, data supporting these studies were not provided. Please provide data from three recent (b) (4) runs in the (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.
7. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 20) regarding the validation of the (b) (4) sterilization process. It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4); however, data supporting these studies were not provided. Please provide data from three recent sterilization runs (b) (4) used for the manufacture of the Copanlisib lyophilisate, 60 mg.
8. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation) and/or Evaluation, pg. 20) regarding the validation of the (b) (4) sterilization process (b) (4) It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4); however, data supporting these studies were not provided. Please provide data from three recent sterilization runs (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.
9. We acknowledge the information provided in module 3.2.P.3.5 regarding the (b) (4) validation of the (b) (4) process used for the manufacture of Copanlisib lyophilisate, 60 mg. However, additional information is required to assess the (b) (4) simulations.

(b) (4)

Nonclinical – Due July 17, 2017
Please explain discrepancies in the study descriptions for Study No. PH-37826 "Multi Cycle Systemic Toxicity Study in Wistar Rats (Administration via Intravenous Infusion, Three/ Four Treatment Cycles (Females/ Males) Followed by a 8~Weeks Recovery Period)". Specifically, as it is mentioned in Sections 1.2 and 2 of the study report and then in the Toxicology Written and Tabulated Summaries in Module 2 of the submission. In the study report, it states BAY 84-1236 was administered via continuous intravenous infusion at dosages of 0, 0.35, 1.15 and 3.46 mg/kg for 4 dosing cycles to 10 male, and for 3 cycles to 10 female Wistar rats per dose group (=main groups). **A cycle comprised three administrations for 1 hour once a week followed by 2 weeks without administration.** However, in the *Toxicology Tabulated Summary* Page 3, it states Cycles being once a week for 3 weeks + 1 week off, and in Section 7.2 there's a description similar to Section 1.2 of the study report. Further in the *Toxicology Written Summary* Table 1-1, Cycles are described as once a week for 3 weeks + 1 week off and then on Page 12, cycles are described as once a week for 3 weeks followed by 8 week recovery. Please submit a memo clarifying all these descriptions to the NDA in module 2 for review by the Pharm/Tox team.

Clinical Pharmacology (QT) – Due July 31, 2017
Please explain why very few are matched between observations in the EG analysis dataset (ADEGM.XPT of Study 18270) and those in the ECG warehouse (Study 16349 and 16270). The rest of the data is acceptable.

There are no pending information requests from clinical or statistics review teams at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The safety review is ongoing. At this time, the review teams have not identified a need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting between you and the review team is currently scheduled for August 15, 2017. 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.

We cannot determine at this time when the labeling/PMR/PMC will the sent to the Applicant.

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/s/

ROMEO A DE CLARO
07/12/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, June 30, 2017 3:51 PM
To: 'Anita Murthy'
Subject: RE: NDA 209936 Aliqopa_FDA Information Request-Response Due July 31 12:00 PM

Hello Anita.

Please see the clarification below:

The datasets (adegm.xpt) were from folders under NDA209936\0001\m5\datasets\16270, and \18270. After transposing the SDTM dataset, numbers of subject and observations were listed in the table, along with the corresponding numbers from those studies in the ECG warehouse. We only found matches from Study 16349, but not 16270. Why were there no corresponding clinical dataset for Study 16270 which had relatively rich ECGs?

Study#	Sub-study	Source	Source	Matched	Unmatched	
		ADEGM.XPT	ECG Warehouse		ADEGM.XPT	ECG Warehouse
		#Subj/#Obs	#Subj/#Obs	#Subj/#Obs	#Subj/#Obs	#Subj/#Obs
16270	16270	26/173	7/1634	0/0	26/173	7/1634
18270	16349	7/304	11/333	7/256	7/39	4/88
	16270	7/48	7/1634	7/0	7/48	7/1634

Please let me know if you have any additional questions.

Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Tuesday, June 27, 2017 12:52 PM
To: Lee-Alonzo, Rosa
Subject: RE: NDA 209936 Aliqopa_FDA Information Request-Response Due July 31 12:00 PM

Dear Rosa – regarding the QT information request from the Division below, Bayer has a/some clarifications to seek in order to provide an appropriate response.

1) Can the Division define what the term "matched between observations" means, specifically, are there any particular observations from the ADEGM.XPT dataset (from Study 18270) that do not match the data from Study 16349 and 16270 in the ECG warehouse.

Regards,

Anita Murthy

From: Lee-Alonzo, Rosa [mailto:Rosa.Lee-Alonzo@fda.hhs.gov]
Sent: Thursday, June 15, 2017 11:17 AM
To: Anita Murthy
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due July 31 12:00 PM

Dear Anita,

Please refer to your new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than **July 31, 2017, 12:00 PM EST**.

QT Information Request
Please explain why very few are matched between observations in the EG analysis dataset (ADEGM.XPT of Study 18270) and those in the ECG warehouse (Study 16349 and 16270). The rest of the data is acceptable.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
07/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

INFORMATION REQUEST

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, Pharm D., Deputy Director Oncology 2
100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated March 16, 2017, received March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliqopa (copanlisib) Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than July 12, 2017**, in order to continue our evaluation of your NDA.

1. We acknowledge the information provided in section 3.2.P.7 which states that a 6 mL colorless glass type 1 vial is used for the primary container closure system. Please provide the manufacturer and a product identification number of the 6 mL glass vial proposed for the container closure system of Copanlisib lyophilisate, 60 mg.

2. We acknowledge the information provided in module 3.2.P.2 regarding container closure integrity validation. We note that (b) (4) [redacted]

3. Please provide a (b) (4) statement for the drug product.

4. We acknowledge the (b) (4) validation information provided in module 3.2.P.3.5 which states that the (b) (4) [redacted]

(b) (4) validation study.

5. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 19) regarding the validation of the stopper sterilization process. It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4) however, data supporting these studies were not provided. Please provide data from three recent stopper sterilization runs (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.

6. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 20) regarding the validation of the (b) (4) process. It is stated that (b) (4) the required sterilization criteria and all endotoxin indicators showed a (b) (4) in endotoxins; however, data supporting these studies were not provided. Please provide data from three recent (b) (4) runs in the (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.

7. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 20) regarding the validation of the (b) (4) sterilization process. It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4); however, data supporting these studies were not provided. Please provide data from three recent sterilization runs (b) (4) used for the manufacture of the Copanlisib lyophilisate, 60 mg.

8. We acknowledge the information provided in module 3.2.P.3.5 (Process Validation and/or Evaluation, pg. 20) regarding the validation of the (b) (4) sterilization process (b) (4) It is stated that (b) (4) the required sterilization criteria and all biological indicators displayed a (b) (4); however, data supporting these studies were not provided. Please provide data from three recent sterilization runs (b) (4) used for the manufacture of Copanlisib lyophilisate, 60 mg.

9. We acknowledge the information provided in module 3.2.P.3.5 regarding the validation of the (b) (4) process used for the manufacture of Copanlisib lyophilisate, 60 mg. However, additional information is required to assess the (b) (4) simulations.

(b) (4)

(b) (4)

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 6/28/2017 03:38:51PM
GUID: 508da7230002a24fd4abdd8018af2a08

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Monday, June 26, 2017 6:40 AM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due June 29, 2017, 4:30 PM

Dear Anita,

Please refer to your submission dated March 16, 2017 for new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than Thursday, **June 29, 2017, 4:30 PM EST**.

Clinpharm IR

1. In Module 2.7.2 Summary of Clinical Pharmacology Studies, you mentioned that clinical studies in patients with moderate hepatic impairment and patients with severe renal impairment are planned. Please update the status of both studies.
2. In part B of Study 16349, 33.8% (48 out of 142) of patients had Grade 1-4 hypoglycemia, provide a two-by-two summary table for hypoglycemia incidence (yes or no) and usage of metformin. Please also provide the % and number of patients taking metformin in Part B.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Let me know if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/26/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/21/2017 07:00:30 PM
To: anita.murthy@bayer.com
CC: luz.e.rivera@fda.hhs.gov; teshara.bouie@fda.hhs.gov; Rosa.Lee-Alonzo@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST NDA 209936

NDA 209936
INFORMATION REQUEST

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K Murthy, Pharm D.
Deputy Director Oncology 2
100 Bayer Blvd
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated December 19, 2016, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliqopa (Copanlisib) Injection.

The Product Quality review team has the following comments and information request. We request a written response by June 30, 2017, in order to continue our evaluation of your submission. Please provide your response via email followed by an official amendment.

1.The acceptance criterion of the (b) (4) degradation product in the drug product release and stability specification appears to be wide. Tighten the proposed release and stability specification limits for the (b) (4) degradation product to (b) (4)%.
2.Update the application with additional stability data on the drug product.

Please acknowledge this communication upon receipt.

If you have any questions, please contact CDR Teshara Bouie at (301) 796-1649, or email

Teshara.Bouie@fda.hhs.gov, or me at (301) 796 4013, email luz.e.rivera@fda.hhs.gov

Best regards,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Thursday, June 15, 2017 11:17 AM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due July 31 12:00 PM

Dear Anita,

Please refer to your new NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than **July 31, 2017, 12:00 PM EST**.

QT Information Request
Please explain why very few are matched between observations in the EG analysis dataset (ADEGM.XPT of Study 18270) and those in the ECG warehouse (Study 16349 and 16270). The rest of the data is acceptable.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/15/2017

Bouie, Teshara

'om:	Bouie, Teshara
ɜent:	Wednesday, June 14, 2017 4:00 PM
To:	anita.murthy@bayer.com
Cc:	Lee-Alonzo, Rosa
Subject:	NDA 209936 - Information Request

Hi Anita,

The CMC team has the following request for information:

1. Provide a list of equipment for comparison, including the size, manufacturer, make and model, used for clinical and proposed for each unit operation of commercial drug product manufacturing.

2. FDA acknowledges the (b) (4) study for selection of suitable material for the (b) (4) We did not see where compatibility of the (b) (4) was addressed. Provide the (b) (4) data to support a (b) (4) compatibility study.

We request a response no later than COB June 22, 2018.

We also request a brief tcon with Bayer to discuss your comparability protocol. We are available Friday June 16, 2017 at 12:30 pm EST. Please let me know if this time works for your team.

ease confirm receipt of this email.

Thanks,

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, United States Public Health Service
Quality Assessment Lead (Acting)
FDA/CDER/OPQ/OPRO
Phone (301) 796-1649
Fax (301) 796-9749

FDA U.S. FOOD & DRUG ADMINISTRATION

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, June 02, 2017 12:37 PM
To: 'Anita Murthy'
Subject: RE: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Hello Anita,

Please see the clarification below:

QT Study Information Request - Clarification
We noticed that ECGs of 18 subjects for Study 16270 had been uploaded to the ECG warehouse. Please upload additional ECGs if more subjects were pooled into the QTc analysis in Study 18270. The reason to request ECGs from Study 16439 and 16790 was that the studies had relatively rich ECGs in the pooled analysis for Study 18270. Please scan the paper ECGs and submit to FDA directly if no digital ECGs are available.

Let me know if you have any other questions.

Rosa

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Friday, June 02, 2017 11:12 AM
To: Lee-Alonzo, Rosa
Subject: RE: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Dear Rosa –

Bayer would like to seek clarification regarding one of the Agency's requests. The Agency requested for Bayer to " upload digital ECGs with annotations for Study 16349, 16790 to the ECG warehouse (www.ecgwarehouse.com)". Study 16790 was a pharmacodynamic study that collected ECG data as part of the routine safety data collection, however study 16270 part B collected ECG data centrally for the purposes of evaluating any effects on QTC from patients treated with copanlisib. Given this, did the Agency want Bayer to provide ECG data from Study 16790 or was this intended to be Study 16270 part B?

Thank you for your help,

Regards,

Anita Murthy

From: Lee-Alonzo, Rosa [mailto:Rosa.Lee-Alonzo@fda.hhs.gov]
Sent: Thursday, June 01, 2017 12:29 PM
To: Anita Murthy
Subject: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Dear Anita,

Please refer to your submission for NDA 209936 Aliqopa.

We request a response to the following FDA **clinical pharmacology** information request no later than **Monday, June 5, 2017 4:00 PM EST**.

1. **Clinical Pharmacology Information Request**
   When we tried to conduct exposure-safety analysis using data from the pivotal trial (Study 16349), an issue was found with Subject ID (SID) of the NONMEM dataset "imp17566-003_fv_cov xpt". For Study 16349, the USUBJID usually ended with "900x" as the last four digits. However, the SIDs of the NONMEM dataset "imp17566-003_fv_cov.xpt" for Study 16349 are all ended with "000x". There is no USUBJID for study 16349 in the NONMEM dataset. Please clarify and submit the revised NONMEM dataset with USUBJIDs that matches those of study 16349. Please address this issue as soon as possible but no later than the due date above.

We request a response to the following FDA **QT Study** information request no later than **Friday, June 9, 2017 4:00 PM EST**.

2. **QT Study Information Request**
   With regards to Study 18270, please update the analysis dataset (copanlisib_qtc_data_v2.xpt) by including PR, QRS intervals, their baseline, and change from baseline values. Secondly, please upload digital ECGs with annotations for Study 16349, 16790 to the ECG warehouse (www.ecgwarehouse.com.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/06/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Tuesday, June 06, 2017 8:14 AM
To: 'Anita Murthy'
Subject: NDA209936 Aliqopa_FDA Information Requests-Response Due June 8, 2017 4:00 PM

Importance: High

Good morning, Anita.

Could you have you team submit the request below by Thursday, June 8, 2017, 4:00 PM EST?

Thank you.

Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

From: Lee-Alonzo, Rosa
Sent: Monday, June 05, 2017 1:26 PM
To: 'Anita Murthy'
Subject: RE: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM
Importance: High

Anita,

Please submit an updated "imp17566-003_fv_cov.xpt" with USUBJID included by COB (4:30 PM EST) today. You may provide your response via email and follow-up with an official submission to the NDA.

Thank you.

Rosa

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Monday, June 05, 2017 10:50 AM
To: Lee-Alonzo, Rosa
Subject: RE: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Dear Rosa – please see Bayer response to Information Request number one. Please let me know if this explanation is acceptable for the reviewer or if additional information is needed.

1. **Clinical Pharmacology Information Request**

When we tried to conduct exposure-safety analysis using data from the pivotal trial (Study 16349), an issue was found with Subject ID (SID) of the NONMEM dataset "imp17566-003_fv_cov xpt". For Study 16349, the USUBJID usually ended with "900x" as the last four digits. However, the SIDs of the NONMEM dataset "imp17566-003_fv_cov.xpt" for Study 16349 are all ended with "000x". There is no USUBJID for study 16349 in the NONMEM dataset. Please clarify and submit the revised NONMEM dataset with USUBJIDs that matches those of study 16349. Please address this issue as soon as possible but no later than the due date above.

Bayer response: The reason that the subject IDs appear different is to distinguish patients from Study 16349 part A and Study 16349 part B. Reference is made to the identifiers in the "Data_definition_file.pdf" which was submitted together with R-11088 (popPK report) in wave 2 of the NDA 209936/eCTD seq 0001 (a courtesy copy attached herein). On page 2 of this pdf document, the agency can find an overview of the data files used in the popPK analysis and the clinical studies that contributed PK data. The first entry in this "Table of contents" refers to "1. Data-files for modelling building and evaluation" and then "1.1 Model-building data file including data from studies 12871, 15205 and 16349 Part A". This points to the file in question which was also submitted, "imp17566-003_fv_cov.xpt". The SID and STUD data items of this file allow each patient to be uniquely identified. The subjects with STUD = 16349 are all part of Study 16349 Part A and the SID ends indeed with "000x". All subjects and all their data are also part of the data file "Cop_PK_all.xpt" listed in the table of content under "1.5 Model-building data file including data from studies 12871, 15205, 16790, 16270 Arm A and 16349 Part B". The popPK analysis and the data file "Cop_PK_all.xpt" (R-11088) also includes study 16349 Part A data (not explicitly mentioned in the title). Again, the data items SID and STUD of the file "Cop_PK_all.xpt" (see p. 13 of 16 of Data_definition_file.pdf) allow each patient to be uniquely identified. The entries for STUD are explained in detail: STUD = 163491 refer to patients of study 16349 Part A and their SID ends with "000x" (see above); STUD = 163492 refers to patients of study 16349 Part B and their SID ends with "900x". In summary, Bayer references "Cop_PK_all.xpt" for the location of all of the data by subject ID for all studies included in the POP PK analyses, including Studies 16349 part B and 16349 part A.

Regards,

Anita Murthy

From: Lee-Alonzo, Rosa [mailto:Rosa.Lee-Alonzo@fda.hhs.gov]
Sent: Thursday, June 01, 2017 12:29 PM
To: Anita Murthy
Subject: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Dear Anita,

Please refer to your submission for NDA 209936 Aliqopa.

We request a response to the following FDA **clinical pharmacology** information request no later than **Monday, June 5, 2017 4:00 PM EST.**

1. **Clinical Pharmacology Information Request**

When we tried to conduct exposure-safety analysis using data from the pivotal trial (Study 16349), an issue was found with Subject ID (SID) of the NONMEM dataset "imp17566-003_fv_cov xpt". For Study 16349, the USUBJID usually ended with "900x" as the last four digits. However, the SIDs of the NONMEM dataset "imp17566-003_fv_cov.xpt" for Study 16349 are all ended with "000x". There is no USUBJID for study 16349 in the NONMEM dataset. Please clarify and submit the revised NONMEM dataset with USUBJIDs that matches those of study 16349. Please address this issue as soon as possible but no later than the due date above.

We request a response to the following FDA **QT Study** information request no later than **Friday, June 9, 2017 4:00 PM EST**.

2. **QT Study Information Request**

With regards to Study 18270, please update the analysis dataset (copanlisib_qtc_data_v2.xpt) by including PR, QRS intervals, their baseline, and change from baseline values. Secondly, please upload digital ECGs with annotations for Study 16349, 16790 to the ECG warehouse (www.ecgwarehouse.com.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/06/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Friday, June 02, 2017 11:43 AM
To: 'Anita Murthy'
Subject: NDA209936 Aliqopa_FDA Information Requests

Good morning, Anita.

Please refer to your submission for NDA 209936 Aliqopa. I will provide you with clarification for the QT Study information request sent yesterday, June 1, 2017 as soon as I hear back from the reviewer. In addition, please see the information requests below:

We request a response to the following FDA **clinical pharmacology** information request no later than **Friday, June 9, 2017 4:00 PM EST**.

1. **Clinical Pharmacology Information Request**
   Make a summary table about the treatment discontinuation reason of each patient in Study 16349, with USUBJID as ID. Please let us know the file name and folder place if the requested information has already been submitted.

We request a response to the following FDA **carton/container** information request no later than **Tuesday, June 13, 2017 4:00 PM EST**.

2. **Carton/Container Information Request**
   Please submit your container labels. We only have the carton labels.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/02/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Thursday, June 01, 2017 12:29 PM
To: 'Anita Murthy'
Subject: NDA209936 Aliqopa_FDA Information Requests-Response Due June 5, 2017 4:00 PM

Dear Anita,

Please refer to your submission for NDA 209936 Aliqopa.

We request a response to the following FDA **clinical pharmacology** information request no later than **Monday, June 5, 2017 4:00 PM EST.**

1. **Clinical Pharmacology Information Request**
   When we tried to conduct exposure-safety analysis using data from the pivotal trial (Study 16349), an issue was found with Subject ID (SID) of the NONMEM dataset "imp17566-003_fv_cov xpt". For Study 16349, the USUBJID usually ended with "900x" as the last four digits. However, the SIDs of the NONMEM dataset "imp17566-003_fv_cov.xpt" for Study 16349 are all ended with "000x". There is no USUBJID for study 16349 in the NONMEM dataset. Please clarify and submit the revised NONMEM dataset with USUBJIDs that matches those of study 16349. Please address this issue as soon as possible but no later than the due date above.

We request a response to the following FDA **QT Study** information request no later than **Friday, June 9, 2017 4:00 PM EST.**

2. **QT Study Information Request**
   With regards to Study 18270, please update the analysis dataset (copanlisib_qtc_data_v2.xpt) by including PR, QRS intervals, their baseline, and change from baseline values. Secondly, please upload digital ECGs with annotations for Study 16349, 16790 to the ECG warehouse (www.ecgwarehouse.com.

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Contact me if you have any questions.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
06/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bayer Healthcare Pharmaceuticals Inc.
100 Bayer Blvd
P.O. Box 915
Whippany, NJ 07981-0915

ATTENTION: Anita K. Murthy, PharmD
Deputy Director Oncology 2

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated and received March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copanlisib for Injection, 60 mg per vial.

We also refer to your correspondence, dated and received March 28, 2017, requesting review of your proposed proprietary name, Aliqopa.

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

If any of the proposed product characteristics as stated in your March 28, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Rosa Lee-Alonzo, Regulatory Project Manager, in the Office of New Drugs at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated March 16, 2017, received March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Aliqopa (copanlisib), 60 mg per vial, sterile lyophilized solid.

We also refer to your amendment dated December 21, 2016.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. The revision date at the end of Highlights must be proceeded by the word "Revised".
2. In the Table of Contents, all section headings must be **bolded**.
3. The cross-references listed in sections 2.1 and 5.6 are not in italics or enclosed within brackets. Ensure all cross-references in the Full Prescribing Information are in the correct format.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 12, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

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

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY C BAIRD
05/24/2017
Signing for Ann T. Farrell, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/22/2017 09:21:59 AM
To: anita.murthy@bayer.com
CC: Teshara.Bouie@fda.hhs.gov, michael.hadwiger@fdsa.hhs.gov
BCC: Rajiv.Agarwal@fda.hhs.gov, Sharon.Kelly@fda.hhs.gov
Subject: Method Verification Material Request for NDA 209936

Good morning,

Please see the attached letter requesting method verification materials for NDA 209936 and confirm receipt of this request to Laura.Pogue@fda.hhs.gov.

Thank you,

Laura C. Pogue, Ph.D.
Method Verification Program (MVP) Coordinator
Division of Pharmaceutical Analysis | Office of Testing and Research
FOOD AND DRUG ADMINISTRATION - CENTER FOR DRUG EVALUATION AND RESEARCH
645 S. Newstead Ave | St Louis, MO 63110
314-539-2155 (w) | Laura.Pogue@fda.hhs.gov (e)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

PRIORITY REVIEW DESIGNATION

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated March 16, 2017, received March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Aliqopa (copanlisib).

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 November 16, 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 August 16, 2017.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before May 29, 2017.

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY C BAIRD
05/15/2017
Signing for Dr. Ann T. Farrell

From: Lee, Jennifer (CDER)
To: "Anita Murthy"
Cc: Lee-Alonzo, Rosa
Subject: RE: NDA 209936 copanlisib -- FDA Information Request Response Due 5/5 4PM EST
Date: Thursday, May 04, 2017 4:04:00 PM
Attachments: image001.png

Hello Anita,

We would prefer both listings (independent as well as local). This would help orient the ORA field staff while on study site.

Thank you,
Jennie

From: Anita Murthy [mailto:anita.murthy@bayer.com]
Sent: Thursday, May 04, 2017 11:35 AM
To: Lee, Jennifer (CDER)
Cc: Lee-Alonzo, Rosa
Subject: RE: NDA 209936 copanlisib -- FDA Information Request Response Due 5/5 4PM EST

Dear Jennie – may I ask a clarification question. For point (c), the Agency is requesting "Primary and other relevant study efficacy endpoint…..".

For Study 16349 part B, the primary endpoint per the protocol is the overall response rate (ORR) as assessed by an independent review committee. Additionally, as a supportive analysis, we collected the overall response rate as assessed by the local investigator.

Would the Agency want a listings (from these two sites by subject) of both the ORR as assessed by the independent committee and the local investigator, or just the ORR by local investigator for the purposes of a potential site audit?

Regards,

Anita Murthy

From: Lee, Jennifer (CDER) [mailto:Jennifer.Lee1@fda.hhs.gov]
Sent: Tuesday, May 02, 2017 8:16 AM
To: Anita Murthy
Cc: Lee-Alonzo, Rosa
Subject: NDA 209936 copanlisib -- FDA Information Request Response Due 5/5 4PM EST

Dear Dr. Murthy,

Please find below a FDA information request for NDA 209936, also referenced in INDs 103,240 and 115,916, for your copanlisib drug application. Please submit your response to this request via e-mail by **4 pm EST, May 5, 2017**, followed by officially submitting the response to the NDA file. Please send your emailed response to me and CC Rosa Lee-Alonzo on the correspondence.

FDA Information Request

- ***Submit the following study subject data listing information grouped as pdf files, for Armando Santoro, M.D. (Site 22005: Milan, Italy under Study Protocol 16349 –Part B)***
  - ***a) Subject discontinuations (If applicable, per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).***
  - ***b) Subject assignment per treatment arm (if applicable).***
  - ***c) Primary and other relevant study efficacy endpoint (if applicable, e.g., palpable liver or spleen lesions, bone marrow biopsy results, cytogenetics, other genetic abnormalities, imaging lesions before and after treatment, date of entry, date of death, prior treatment dates, survival calendar time points).***
  - ***d) Concomitant medication list (non-study medications).***
  - ***e) All adverse events (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).***
  - ***f) Laboratory relevant assessments to support the efficacy endpoint responses, other the items specified in item c) above.***
  - ***g) Any protocol deviations or violations.***

- ***Submit the above requested information for Luigina Mollica, M.D. (Site 26003: Quebec, Canada, also under Study Protocol 16349 –Part B).***

- ***Confirm that your clinical trial data files are located at your headquarters in Whippany, NJ, should the Agency determine the necessity of a sponsor site audit.***

Please confirm receipt of this information request.

Kind regards,
Jennie

_____

Jennifer J. Lee, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

JENNIFER J LEE
05/04/2017

From:	Lee, Jennifer (CDER)
To:	"Anita Murthy"
Cc:	Lee-Alonzo, Rosa
Subject:	NDA 209936 copanlisib -- FDA Information Request Response Due 5/5 4PM EST
Date:	Tuesday, May 02, 2017 8:15:00 AM
Attachments:	image013.png

Dear Dr. Murthy,

Please find below a FDA information request for NDA 209936, also referenced in INDs 103,240 and 115,916, for your copanlisib drug application. Please submit your response to this request via e-mail by **4 pm EST, May 5, 2017**, followed by officially submitting the response to the NDA file. Please send your emailed response to me and CC Rosa Lee-Alonzo on the correspondence.

FDA Information Request

- ***Submit the following study subject data listing information grouped as pdf files, for Armando Santoro, M.D. (Site 22005: Milan, Italy under Study Protocol 16349 –Part B)***
  - ***a) Subject discontinuations (If applicable, per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).***
  - ***b) Subject assignment per treatment arm (if applicable).***
  - ***c) Primary and other relevant study efficacy endpoint (if applicable, e.g., palpable liver or spleen lesions, bone marrow biopsy results, cytogenetics, other genetic abnormalities, imaging lesions before and after treatment, date of entry, date of death, prior treatment dates, survival calendar time points).***
  - ***d) Concomitant medication list (non-study medications).***
  - ***e) All adverse events (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).***
  - ***f) Laboratory relevant assessments to support the efficacy endpoint responses, other the items specified in item c) above.***
  - ***g) Any protocol deviations or violations.***

- ***Submit the above requested information for Luigina Mollica, M.D. (Site 26003: Quebec, Canada, also under Study Protocol 16349 –Part B).***

- ***Confirm that your clinical trial data files are located at your headquarters in Whippany, NJ, should the Agency determine the necessity of a sponsor site audit.***

Please confirm receipt of this information request.

Kind regards,
Jennie

_____

Jennifer J. Lee, PharmD

Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Hematology Products
U.S. Food and Drug Administration
Tel: 240-402-4622
jennifer.lee1@fda.hhs.gov

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/s/

JENNIFER J LEE
05/02/2017

Lee-Alonzo, Rosa

From: Lee-Alonzo, Rosa
Sent: Wednesday, April 19, 2017 3:44 PM
To: 'Anita Murthy'
Subject: NDA 209936 Aliqopa_FDA Information Request-Response Due April 25 by 5:00 PM EST

Dear Anita,

Please refer to your submission dated March 16, 2017 for NDA 209936 Aliqopa.

We request a response to the following FDA information request no later than **Tuesday, April 25, 2017 by 5:00 PM EST.**

Information Request:

To facilitate the selection of the clinical sites for inspection, submit a dataset (1 site per row) with the following information from clinical trial 16349 – Part B. Submit this information as a SAS transport file, and include a define.pdf file

- Site number
- Principal investigator
- Location: Address, City, State, Country
- Contact Information: Name, Phone, Fax, Email
- Number of subjects screened
- Number of subjects enrolled
- Number of subjects who received Copanlisib
- Number of subjects who achieved complete response (CR) or partial response (PR), per investigator
- Number of subjects who achieved CR, per investigator
- Number of subjects who achieved CR or PR, per independent review committee
- Number of subjects who achieved CR, per independent review committee
- Number of major protocol violations
- Number of deaths
- Number of subjects who experienced serious adverse events (SAEs)

Please confirm receipt, provide your response via email, and follow-up with an official submission to the NDA.

Contact me if you have any questions.

Thank you.

Best regards,
Rosa

Rosa J. Lee-Alonzo, PharmD
Regulatory Project Manager

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

Tel: 301-348-3004
rosa.lee-alonzo@fda.hhs.gov

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/s/

ROSA J LEE-ALONZO
04/19/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

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

Name of Drug Product: Aliqopa (copanlisib)

Date of Application: March 16, 2017

Date of Receipt: March 16, 2017

Our Reference Number: NDA 209936

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 May 15, 2017, in accordance with 21 CFR 314.101(a).

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

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

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

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

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Rosa Lee-Alonzo, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROSA J LEE-ALONZO
03/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

PROPRIETARY NAME ACKNOWLEDGEMENT

Bayer Healthcare Pharmaceuticals Inc.
100 Bayer Blvd
P.O. Box 915
Whippany, NJ 07981-0915

ATTENTION: Anita K. Murthy, PharmD
Deputy Director Oncology 2

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated and received March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copanlisib Injection, 60 mg.

We acknowledge receipt of your correspondence, dated and received March 28, 2017, requesting a review of your proposed proprietary name, Aliqopa.

If the application is filed, the user fee goal date for your proposed proprietary name review will be June 26, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Rosa Lee-Alonzo, Regulatory Project Manager, in the Office of New Drugs at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
03/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

ACKNOWLEDGE PRESUBMISSION

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

We have received your presubmission of product quality and non-clinical information for the following:

Name of Drug Product: Aliqopa (copanlisib)

Date of Submission: December 21, 2016

Date of Receipt: December 21, 2016

Our Reference Number: NDA 209936

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

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

If you have any questions, call me at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Rosa Lee-Alonzo, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROSA J LEE-ALONZO
12/30/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115916

MEETING MINUTES

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director
100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Bay 80-6946, BAY 84-1236.

We also refer to the meeting between representatives of your firm and the FDA on October 18, 2016. The purpose of the meeting was to discuss the Phase 2 Study 16349 part B and results which enrolled patients with indolent non-Hodgkin's lymphoma (iNHL) including follicular lymphoma (FL) and marginal zone lymphoma (MZL), to determine if the study as well as the results support filing copanlisib under sub-part H for (b) (4) the nonclinical package adequacy to support the New Drug Application (NDA) filing, and format and content of the planned NDA.

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 Natasha Kormanik, Regulatory Health Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Acting Supervisory Associate Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	pre-NDA
Meeting Date and Time:	October 18, 2016 from 9:00 AM -10:00 AM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 115916
Product Name:	BAY 80-6946, BAY 84-1236
Indications	(1) Treatment of patients with relapsed (b) (4) follicular lymphoma (FL) who have received at least two prior therapies and (b) (4)
Sponsor/Applicant Name:	Bayer HealthCare Pharmaceuticals Inc.
Meeting Chair:	Albert Deisseroth, MD, PhD
Meeting Recorder:	Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Albert Deisseroth, MD, PhD – Acting Supervisory Associate Director
Ashley Ward, MD – Clinical Reviewer
Theresa Carioti, MPH – Chief, Project Management Staff
Michael Gwathmey, RN – Regulatory Health Project Manager
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology
Pedro DelValle, PhD – Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V
Stacy S. Shord, PharmD – Team Leader
Sriram Subramaniam, PhD – Reviewer

Office of Clinical Pharmacology/Division of Pharmacometrics
Nitin Mehrotra, PhD – Pharmacometrics Team Leader, Review Team 2

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD – Biometrics Team Leader
Kallappa Koti, PhD – Reviewer

SPONSOR ATTENDEES

Bayer HealthCare Pharmaceuticals, Inc.
Jose Garcia Vargas, MD – Clinical Development
Barry Childs, MD – Clinical Development
Camille Granvil, PhD – Clinical Pharmacology
Zuzana Jirakova Trnkova, MD, PhD – Clinical Pharmacology
Hui-Talia Zhang, MD, ScD – Pharmacovigilance
Pamela Gilles, PhD – Toxicology
Florian Hiemeyer, MS – R&D Statistics
Michael Shan, PhD – R&D Statistics
Anita K. Murthy, PharmD – Regulatory Affairs
Todd Paporello, BS – Regulatory Affairs
Philip Johnson, MBA – Regulatory Affairs
Gerhard Schlueter, PhD – Regulatory Affairs
Emiko Tsuruta, BS – Regulatory Affairs
Melissa Thomas, MBS – Program Management

(b) (4)

1.0 BACKGROUND

On September 15, 2016, Bayer HealthCare Pharmaceuticals Inc. requested a pre-NDA meeting to discuss with the Agency the following:

1. To discuss with the Agency the Phase 2 Study 16349 part B and results,which enrolled patients with indolent Non Hodgkins Lymphoma (iNHL) including follicular lymphoma (FL) and marginal zone lymphoma (MZL), as well as supporting data package (phase 1, phase 2A) to determine if the study as well as the results support filing copanlisib under sub-part H for (b) (4)
2. To reach agreement with the Agency that the nonclinical package is adequate to support the NDA filing.
3. To reach agreement with the Agency on certain aspects of the format and content of the planned NDA.

The Sponsor states that copanlisib is a novel, highly selective, (b) (4) phosphatidylinositol 3 kinase (PI3K) inhibitor with potent activity against both the α and δ isoforms. The Sponsor is proposing an indication for the treatment of patients with relapsed (b) (4) follicular lymphoma (FL) who have received at least two prior therapies (b) (4)

FDA sent Preliminary Comments to Bayer HealthCare Pharmaceuticals Inc. on October 14, 2016.

2.0 DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree that the data from Study 16349 Part B support a filing of an NDA under 21CFR314 sub-part H for copanlisib in the treatment of FL in patients who are relapsed (b) (4) to 2 prior therapies?

FDA Response to Question 1: *The FDA is encouraged by the data that have been presented in the pre-meeting package, but the adequacy of the data to support the submission of a marketing application would be determined in the filing review. Trials in relapsed or refractory follicular lymphoma that are not randomized and that have a primary endpoint considered reasonably likely to predict clinical benefit (i.e., an endpoint other than survival) would typically be used to support accelerated approval under 21 CFR 314 Subpart H. Whether or not your data could be used to support an accelerated approval in this indication would be determined at the time of regulatory action.*

Discussion: No discussion.

Question 2a: Does the Agency agree that (b) (4)

FDA Response to Question 2a: *Yes.*

Discussion: No discussion.

(b) (4)

(b) (4)

Discussion: No discussion.

Question 3: Can the Agency confirm that either of these studies (Study 17067 or Study 17833) is acceptable to serve as the confirmatory study in accordance with 21CFR314 sub-part H?

FDA Response to Question 3: *The suitability of Study 17067 and/or Study 17833 to serve as a confirmatory study in accordance with 21CFR314 sub-part H cannot be determined at this time. The Agency is concerned that subjects with indolent lymphoma treated with copanlisib in combination with rituximab or rituximab and chemotherapy may be at high risk of serious and/or fatal toxicities, as several recent Phase 3 studies of idelalisib in similar combination regimens in a similar patient population were recently halted because of excess deaths and serious adverse events among patients treated in the idelalisib-containing groups (Cheah and Fowler, Blood 2016, 128:331). We strongly encourage you to consider including an interim analysis for safety on CHRONOS-3 and CHRONOS-4. If you submit data from Study 16349 Part B in support of a marketing application, we suggest that you include a discussion of your contingency plan for fulfilling the requirements of 21CFR314 sub-part H should CHRONOS-3 and CHRONOS-4 fail.*

In addition, we are concerned about the slow rate of enrollment on these studies. We suggest that you provide further detailed information about accrual to date and your plan to complete the studies within a reasonable time frame.

Please also note that a confirmatory trial in (b) (4)

(b) (4)

Discussion: The Sponsor provided additional details regarding the enrollment status of CHRONOS-3 and CHRONOS-4. In addition they further explained the interim safety monitoring via the DMC for both studies. The Agency agreed that the safety monitoring plan seems sufficient at this time.

Question 4a: Does the Agency agree that the proposed safety content for the 90-(-120) day safety update report content proposed is acceptable?

FDA Response to Question 4a: *No. The acceptability of the proposed data cut-off date will be determined during the filing review of the initial submission, although tentatively appears appropriate based on the information you have provided to date. In addition to the proposed content, the 90-day safety update should contain updated adverse event and laboratory datasets for all studies, as well as narratives and case report forms for each patient who died*

(regardless of timing of death related to study treatment) or did not complete the study due to an adverse event on all studies. Please note that your safety update should provide cumulative data (from the start of each study) for all studies, with an updated cut-off date compared to that provided in the NDA, and not just the new information.

Discussion: The Agency agreed as part of the safety update, the Sponsor will be required to submit updated adverse event and laboratory data sets for study 16349. The Agency also clarified that it does not expect un-blinded safety data from CHRONOS-2, CHRONOS-3, and CHRONOS-4.

Question 4b: Does the Agency agree with the proposed efficacy data planned to be included in the 90-(-120) day safety update?

FDA Response to Question 4b: *No. The application should be complete upon submission.*

Discussion: No discussion

2.2. Clinical Pharmacology

Question 5: Does the Agency agree with the proposal for provision of QTc data for copanlisib to support an NDA filing?

FDA Response to Question 5: *The QTc data from Studies 12871, 15205 and 16349 proposed to support the original NDA submission is insufficient to characterize the QTc effects of copanlisib. Studies 12871 and 15205 provided only very limited ECG sampling with an inadequate description of the study results according to E14 guidance and Study 16349 only included 6 subjects with QTc sub-study (Part B). Additionally, you previously stated that you were unable to collect sufficient time-matched PK and ECG data from Study 16349. The QTc evaluation from Study 16270 should be included with the original NDA submission, as the Agency previously found the study design adequate to detect a large QT effect of 20 msec.*

Discussion: The Agency recommended that the Sponsor include the proposed pooled analysis, concentration QT analysis, and integrated safety analysis to support the original NDA submission. The adequacy of this analysis will be a review issue. Additionally, the Sponsor should provide a detailed plan for the post-marketing study.

Question 6: Does the Agency agree that the popPK analysis is sufficient to support the clinical dosing recommendations for the copanlisib in special populations (hepatic and renal impairment?

FDA Response to Question 6: *Your dosing recommendations for patients with mild hepatic impairment and mild, moderate or severe renal impairment appear reasonable; however, the final determination of the acceptability of your proposals will be made following comprehensive review of the pharmacokinetic and safety data, and overall risk-benefit assessment. Your proposal to use copanlisib* (b) (4)

(b) (4)

Since your mass balance data indicates that the pharmacokinetics of copanlisib is likely to be affected by hepatic impairment, you should conduct a dedicated hepatic impairment study per the FDA draft Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf.**

You should propose the hepatic impairment study as a post marketing requirement (PMR), including study synopsis and major milestones (e.g., study completion date, submission of final study report), for FDA review at the time of NDA submission.

Discussion: No discussion.

Question 7: Is this acceptable to the Agency?

FDA Response to Question 7: *Yes, your proposal for concomitant use of strong CYP3A inhibitors and inducers appears reasonable; however, a final determination will be made following review of the totality of evidence in the NDA.*

Discussion: No discussion.

2.3. Non-Clinical

Question 8: Does the Agency agree that the nonclinical program is adequate to support the market authorization of copanlisib (b) (4) under 21CFR214 part H?

FDA Response to Question 8: *No. An NDA must contain all necessary data and information to fulfill the regulatory requirements for nonclinical evaluation of your proposed product. It appears the duration of your chronic repeat-dose toxicity study is not sufficient to support marketing (see ICH S9).*

Discussion: The Sponsor mentioned they conducted a 13 week repeat dose study that could satisfy the requirement per ICH S9. The Agency requested a study report to be submitted to the IND for review. The acceptability of this study will be a review issue.

2.4 Administrative

Question 9: The proposed content and format for section 2.7.3 and of the ISS 5.3.5.3 with narrative portion being located in 2.7.4 is aligned with FDA guidance "Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Documents*" (April 2009)" for the planned NDA. Is this proposed content and format for the ISS and proposed no ISE acceptable to the Agency?

FDA Response to Question 9: *We agree with your plan to submit an SCE with all required elements of the ISE in lieu of an ISE as long as the document does not exceed the page limitation for the SCE and contains all of the required analyses of the ISE. Please see "Integrated Summary of Effectiveness: Guidance for Industry" at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf.

The adequacy of the content of the SCE will be assessed during the filing review of the NDA submission, but should include a thorough discussion of all studies of copanlisib in patients with indolent lymphoma, including 17792 and 16790 in addition to the studies that you mentioned (16349 Parts A and B and 12871).

We do not agree with your proposal to include in the ISS only those studies that are company sponsored, administer copanlisib as a single agent and have a primary completion (with clean database) or interim clean database. The ISS should include a detailed analysis of safety in all of your clinical trials, as well as the published literature and any other unpublished reports you may have.

We do not agree with your proposed analysis pools for the ISS. Pool 1 appears acceptable, although it should include patients with indolent lymphoma treated with monotherapy on Study 17792 in addition to the stated studies. For the FL indication, you should limit this pool to subjects with the proposed indication (i.e., relapsed (b) (4) *follicular lymphoma). Pool 2 should include safety data from subjects with any malignancy exposed to copanlisib monotherapy (Studies 12871, 16790, 15205, 17792, 16349 Parts A and B, 17119 and 17120). Pool 3 should include all subjects that have received copanlisib, either as monotherapy or in combination with other agents, and should include studies of healthy volunteers (Study 12871, 16790, 15205, 17792, 12874, 12875, 12876, 16353, 16270, 16349 Parts A and B, 17119 and 17120). Given that your NDA will be based on very early studies, it is essential to maximize the safety data available for review. This pool allows examination of differences among population subsets not possible with the relatively small numbers of patients in the other pools, and evaluation of serious adverse effects too rare to be seen in single studies. You should submit a single ISS dataset that includes integrated data from all studies, with a variable that indicates the population (e.g., FL, MZL, CLL, DLBCL, MCL, solid tumor, healthy volunteer) for easy sorting during the review.*

Your proposal to refer to Module 2.7.4 for the text portion of the ISS is acceptable, as long as the document does not exceed the page limitation for the SCS and contains all of the required analyses of the ISS.

Discussion: The Sponsor proposes to include all studies in the integrated summary of safety with the exception of study 17120 and study 17792. The summary of safety from the two studies will be included in the SCS.

Post-Meeting Comment: The Agency must be able to pool data across trials in various permutations for our analysis. This is typically done using the ISS dataset, which generally contains data from all subjects on all trials submitted as part of the

application. However, it can be done by manually joining datasets from individual trials, as long as the datasets use the same variables (e.g., "Variable X" is the unique subject identifier and "Variable Y" is the verbatim adverse event term across all datasets), and have variables that allow easy adjustments to pooling as the analysis requires (e.g., a variable for the study, a variable for the diagnosis, a variable indicating assigned dose). If individual trial datasets meet these criteria to allow for post-hoc pooling, it is acceptable to submit them individually rather than in the pooled ISS dataset.

The prospective choice of pools for your analysis of safety data is not an exact science. Your analyses of the data in the SCS/ISS may describe the data using pools that make sense to you, but you should ensure that your analyses are sufficient to identify rare safety signals, to identify signals that may occur only in subpopulations of patients, and to comprehensively examine safety from all patients that receive copanlisib, including those that received copanlisib in combination with other agents as well as healthy volunteers.

Question 10: Does the Agency agree with the outline proposed regarding the scope, format, and documentation of the electronic datasets to be submitted?

FDA Response to Question 10: *No. You should submit complete datasets from each clinical trial being used to support the safety and efficacy of copanlisib in the proposed indication. In this case, due to the limited data available for the use of copanlisib in the proposed indication, you should submit complete datasets (final or interim) from all ongoing or completed clinical trials of copanlisib. Your proposal to submit STDM datasets with define.xml, define.pdf, annotated CRF and Study Data Reviewer's Guide, as well as ADAM datasets with define.pdf and Analysis Data Reviewer's Guide is acceptable.*

Discussion: The Sponsor clarified their intent to submit STDM/ADAM data sets for study 16349 parts A and B and analysis data sets for all other copanlisib studies except the three phase 3 studies, study 17120 and study 17792. The Agency agreed with this approach. The Agency reminded the Sponsor that the appropriateness of the data cut-off date will depend of the timing of the submission.

Additional Comments

Clinical

1. In the briefing package, you mention that the proposed data cutoff date for Study 16349 Part A is 01-OCT-2015, and that the proposed data cutoff date for Study 16349 Part B is 22-JUN-2015. Assuming a Q1 2017 submission, the proposed data cutoff date of 22-JUN-2015 for Study 16349 Part B is acceptable. You should use the same data cutoff date for all studies included in the submission (including Study 16349 Part A), unless there is a compelling rationale for an earlier date (e.g., no subsequent data was collected), to ensure that your submission contains complete information. Please provide a table of data cutoff dates for the

other studies that will be included in the submission, with justification for cutoff dates other than 22-JUN-2015 as needed.

2. In the draft Table of Contents for the NDA, please:
   - Explain the inclusion of an amended CSR for Study 12871. If the two planned CSR submissions for Study 12871 include an interim and a final CSR, please note that it is preferable to submit only a final CSR. If an amendment was required after finalization of the CSR, it is preferable to explain the purpose and give a description of the changes made in the amendment as a preface or an appendix to the final CSR.
   - Explain the inclusion of three different CSRs for Study 16349 Part A. If two of the three planned submissions for Study 12871 are interim CSRs, please note that it is preferable to submit only a final CSR.
   - Include an interim CSR for Studies 17792, 17119 and 17120. It is understood that these studies are in progress and that only limited data will be available for your analysis.

Discussion: The Sponsor clarified that a final CSR will be provided for 17119. The Agency agreed that an interim CSR is not required for 17792 or 17120.

Post-Meeting Comment: The FDA notes that an important criterion for an accelerated approval is whether the ORR results from Study 16349 represent a meaningful advantage over available therapies, and this issue was not discussed by the Sponsor in the briefing material submitted to the FDA before the meeting nor in the meeting itself. Accordingly, such a discussion should be an important part of the filing of an NDA that was proposed by the Sponsor.

Clinical Pharmacology

1. In the Summary of Clinical Pharmacology, address the following:
   - The basis for selecting the dose and dosing regimen used in the registration trial.
   - The exposure-safety and exposure-efficacy relationships.
   - Assessment of the potential for copanlisb to prolong the QT/QTc interval, and the conclusion and proposed labeling description.
   - Characteristics of absorption, distribution, and elimination.
   - Influence of intrinsic factors (such as sex, race, weight, disease, organ impairment) and extrinsic factors (such as drug interactions, diet) on copanlisb exposure, efficacy and safety. Recommended dose modifications.

2. In addition, apply the following advice in preparing the clinical pharmacology sections of the original NDA submission:
   a. Submit bioanalytical methods and validation reports for all clinical pharmacology studies.
   b. Provide complete pharmacokinetic datasets for all clinical pharmacology studies. The patients' unique ID in the pharmacokinetic datasets should be consistent with those in datasets submitted for clinical review.
      - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a

define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- Identify individual patient with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose in the Summary of Clinical Pharmacology.

c. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the final reports for all clinical pharmacology studies.

d. Submit information and data to support the population pharmacokinetic analysis. Refer to the pharmacometric data and models submission guidelines found at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm and the Guidance for Industry found at. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for more information.

e. Submit the results of exposure-response (measures of effectiveness, biomarkers and toxicity) analyses for copanlisb in the to-be-indicated patient population in the NDA submission. Include an assessment of the effect of covariates on the exposure-response relationships. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

Discussion: **No discussion.**

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was not discussed. The Sponsor will submit a plan at a later date with timelines in addition to a request for a rolling review.

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

- A preliminary discussion on the need for a REMS was held and it was concluded that it will be a review issues.

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.

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

No issues requiring further discussion

5.0 ACTION ITEMS

Action Item/Description	Owner
Study report to be submitted under IND	Sponsor
Proposal of rolling review and NDA application timeline	Sponsor
PMR proposal	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's PowerPoint presentation.

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/s/

ALBERT B DEISSEROTH
10/20/2016

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209936

LATE-CYCLE MEETING MINUTES

Bayer HealthCare Pharmaceuticals Inc.
Attention: Anita K. Murthy, PharmD
Deputy Director Oncology 2
100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Murthy:

Please refer to your New Drug Application (NDA) dated March 16, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aliqopa (copanlisib).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 15, 2017.

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

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Cross Discipline Team Leader
Division of Hematology Products
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: August 15, 2017, 10:00 AM – 11:00 AM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: NDA 209936
Product Name: ALIQOPA (copanlisib)
Applicant Name: Bayer HealthCare Pharmaceuticals Inc.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Rosa Lee-Alonzo, PharmD

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Barry W. Miller, Acting Deputy Director for Safety
R. Angelo de Claro, MD, Cross Discipline Team Leader
Nicholas Richardson, DO, Clinical Reviewer
Laurel Menapace, MD, Clinical Reviewer
Rosa Lee-Alonzo, PharmD, Regulatory Project Manager
Esther Park, PharmD, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD, Acting Pharmacology/Toxicology Team Leader
Pedro Del Valle, PhD, Pharmacology/Toxicology Reviewer (on phone)

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Guoxiang (George) Shen, PhD, Clinical Pharmacology Reviewer

Office of Clinical Pharmacology/Division of Pharmacometrics
Jiang Liu, PhD, MS, Pharmacometrics Team Leader
Hongshan Li, PhD, Pharmacometrics Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPh, Statistical Team Leader
Xin (Cindy) Gao, PhD, Statistical Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Sherita McLamore-Hines, PhD, Acting Quality Assessment Leader

APPLICANT ATTENDEES

Bayer HealthCare
Anita K Murthy, PharmD, Regulatory affairs
Todd Paporello, PharmD, Regulatory affairs
Yuchao Xie, PhD, Regulatory affairs
Camille Granvil, PhD, Clinical Pharmacology
Zuzana Jirakova Trnkova, MD, PhD, Clinical Pharmacology
Jose Garcia-Vargas, MD, Clinical
Barry Childs, MD, Clinical
Andreas Lender, PhD, CMC
Olaf Doehr, PhD, Nonclinical
Ashok Miriyala, MD, Pharmacovigilance
Hui-Talia Zhang, MD, Pharmacovigilance
Florian Heimeyer, MS, Biostatistics
Melissa Thomas, MS, Project Management
On phone
Joseph Scheeren, PharmD, Global Head of Regulatory Affairs Pharma and Consumer

1.0 BACKGROUND

NDA 209936 was submitted on March 16, 2017 for ALIQOPA (copanlisib).

Proposed indication: Adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies

PDUFA goal date: November 16, 2017

FDA issued a Background Package in preparation for this meeting on August 9, 2017.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments

Refer to separate communication regarding recommended Postmarketing Requirements sent on August 9, 2017.

Discussion: Regarding PMR-2, the Agency notes that the control arm (rituximab + placebo) may not be applicable to the US population. The Agency would consider fulfillment of both PMR-1 and PMR-2 to support a regular approval. Alternatively, the Agency would consider fulfillment of PMR-1 to support regular approval.

Regarding PMR-3, the Agency has no objections with the Applicant's proposal to use extended follow-up from ongoing copanlisib clinical trials to fulfill PMR-3. The Agency clarified that the sample size of 400 was determined through consideration of maximum confidence intervals for specific adverse event rates. The Agency requested the Applicant to provide clarification on the proposed availability of long-term safety data from ongoing trials in order to determine appropriate timelines for the interim reports. The Agency clarified that the long-term safety issues of interest include known adverse events such as pneumonitis, cytopenia, etc. and assessment for potential longer-term safety issues such as cardiovascular complications. The Agency does not have objections with inclusion of patients outside of the US and patients with other hematologic malignancies in the safety database for PMR-3 as long as the Applicant is able to provide justification of the relevance of the findings of the proposed population to the US population. The Agency considers provision of interim reports Year 1, 2, and 3 to be important.

Regarding PMR-4, the Applicant will provide the initial preliminary report including data with subjects with moderate hepatic impairment and severe renal impairment. Updated and final study reports will be submitted including those subjects with severe hepatic impairment.

(b) (4)

3. Major labeling issues

Please see comments in the draft prescribing information sent on August 7, 2017.

Discussion: The Applicant requested clarification of the Agency's objection of using the term (b) (4) **to describe hypertension and hyperglycemia. The Agency plans to address the Applicant's concern during the labeling negotiations.**

4. Review Plans

The Agency plans to complete the review within the PDUFA timeline.

Discussion: The Agency informed the Applicant that an earlier action date (approximately September 18, 2017) may be possible pending resolution of issues regarding labeling and PMRs/PMCs. The Agency would support submission of PLAIR at this time.

5. 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.

Discussion: There was no discussion.

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/s/

ROMEO A DE CLARO
08/15/2017