APPLICATION NUMBER:

210259Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 210259 SUPPL # HFD #

Trade Name: Calquence

Generic Name: acalabrutinib

Applicant Name: Acerta Pharma, B.V.

Approval Date, If Known October 31, 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 years

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

YES ☐  NO ☑️

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

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

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

YES ☑️  NO ☐

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

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

1. Single active ingredient product.

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

YES ☐  NO ☑️

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

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?
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

Investigation #2

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

Investigation #2
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

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Investigation #2

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<th>YES</th>
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<th>Explain:</th>
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</table>

(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: Ashley Lucci Vaughn, MS
Title: Regulatory Project Manager
Date: October 31, 2017

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ASHLEY S LUCCI VAUGHN
10/31/2017

ALBERT B DEISSEROTH
10/31/2017
## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION

<table>
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<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
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<th>Acerta Pharma B.V.</th>
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<tr>
<th>Agent for Applicant:</th>
<th>Ashley Lucci Vaughn, MSc.</th>
</tr>
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<tr>
<th>Division:</th>
<th>Division of Hematology Products</th>
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### NDA Application Type: | 55(b)(1) | 55(b)(2) |
|-------------------------|---------|---------|
### Efficacy Supplement: | 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.

### BLA Application Type: | 351(k) | 351(a) |
|------------------------|--------|--------|
### Efficacy Supplement: | No changes | New patent/exclusivity (notify CDER OND IO) |
Date of check: |

### Actions

- Proposed action is October 31, 2017
- User Fee Goal Date is February 13, 2018
- Previous actions (specify type and date for each action taken) | None |

### Application Characteristics

- If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? | 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/ucm69965.pdf). If not submitted, explain __________

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

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

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

Reference ID: 4174711
Review priority:  □ Standard  □ Priority
Chemical classification (new NDAs only): Type 1 New Molecular Entity
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H
- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)
- Approval based on animal studies
- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

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

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

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  □ Yes  □ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    □ Yes  □ No
  - Indicate what types (if any) of information were issued
    - None
    - FDA Press Release
    - FDA Talk Paper
    - CDER Q&As
    - Other Burst

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    □ No  □ Yes
  - If so, specify the type

- 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) [link]
  □ Included

- Documentation of consent/non-consent by officers/employees [link]
  □ Included

Reference ID: 4174711
## Action Letters

- Copies of all action letters (*including approval letter with final labeling*)
  - Approval 10/31/2017

## Labeling

<table>
<thead>
<tr>
<th>Description</th>
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<tr>
<td>Package Insert (<em>write submission/communication date at upper right of first page of PI</em>)</td>
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</tr>
</tbody>
</table>
  - 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*) |
  - 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*) | ☒ Included 09/27/2017 |
  - Most recent draft labeling | |
| Proprietary Name |
  - Acceptability/non-acceptability letter(s) (*indicate date(s)*) | Letter: 8/25/2017
  - Review(s) (*indicate date(s)*) | Review: 8/24/2017 |
| Labeling reviews (*indicate dates of reviews*) | |

## Administrative / Regulatory Documents

<table>
<thead>
<tr>
<th>Description</th>
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<tr>
<td>RPM Filing Review<strong>4</strong>/Memo of Filing Meeting (<em>indicate date of each review</em>)</td>
<td>8/01/2017</td>
</tr>
<tr>
<td>All NDA 55(b)(2) Actions: Date each action cleared by 55(b)(2) Clearance Committee</td>
<td>☐ Not a (b)(2)</td>
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<tr>
<td>NDAs/NDA supplements only: Exclusivity Summary (<em>signed by Division Director</em>)</td>
<td>☒ Completed</td>
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<td>Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
<td></td>
</tr>
</tbody>
</table>
  - Applicant is on the AIP | ☐ Yes ☒ No |

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

Reference ID: 4174711
This application is on the AIP
- Yes □  No ☒
  - If yes, Center Director’s Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)*

**Pediatrics (approvals only)**
- Date reviewed by PeRC ______
  - If PeRC review not necessary, explain: Orphan drug designation

**Breakthrough Therapy Designation**
- □ N/A
  - Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)
    - Granted 7/31/2017
  - CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*
    - 7/28/2017
  - 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)*
    - N/A

- (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)*

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)
- 7/24/2017

**Minutes of Meetings**
- If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*
  - □ N/A or no mtg
  - ☒ No mtg
    - Preliminary meeting comments issued 5/26/2017; cancelled 6/2/2017 pre-NDA meeting
  - Pre-NDA/BLA meeting *(indicate date of mtg)*
    - 3/21/2016
  - EOP2 meeting *(indicate date of mtg)*
    - 9/0/2017
  - Mid-cycle Communication *(indicate date of mtg)*
    - 9/29/2017
  - Late-cycle Meeting *(indicate date of mtg)*
    - CMC: 8/17/2017
      - EOP1: 10/10/2014
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*
    - (2); 8/17/2017; 8/16/2017; 8/11/2017; 8/10/2017; 8/7/2017; 8/04/2017; 8/3/2017; 8/01/2017 (3); 7/31/2017; 7/27/2017; 7/24/2017; 7/21/2017; 7/18/2017; 6/22/2017; 6/21/2017; 6/20/2017
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<tr>
<th>Decisional and Summary Memos</th>
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<tr>
<td>Office Director Decisional Memo (indicate date for each review)</td>
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<tr>
<td>Division Director Summary Review (indicate date for each review)</td>
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<td>Cross-Discipline Team Leader Review (indicate date for each review)</td>
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<td>PMR/PMC Development Templates (indicate total number)</td>
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<tr>
<td>Clinical Reviews</td>
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<tr>
<td>Clinical Team Leader Review(s) (indicate date for each review)</td>
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<td>Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
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<td>Risk Management</td>
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<td>REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</td>
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<td>REMS Memo(s) and letter(s) (indicate date(s))</td>
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<td>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)</td>
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<td>OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
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**Clinical Microbiology**

- 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**

- Statistical Division Director Review(s) (indicate date for each review) | No separate review |
- Statistical Team Leader Review(s) (indicate date for each review) | No separate review |
- Statistical Review(s) (indicate date for each review) | No separate review |

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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).
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<td>Environmental Assessment (check one) (original and supplemental applications)</td>
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<td>- Categorical Exclusion <em>(indicate review date)</em> <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>See Executive Summary review 10/17/2017 page 06</td>
</tr>
<tr>
<td>- Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>- Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td>Facilities Inspection</td>
<td></td>
</tr>
<tr>
<td>- Facilities inspections <em>(indicate date of recommendation)</em> <em>(within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter)</em> <em>(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
<td>Acceptable</td>
</tr>
<tr>
<td></td>
<td>Withhold recommendation</td>
</tr>
<tr>
<td></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

[^6]: Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ For all 55(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric</td>
<td></td>
</tr>
<tr>
<td>exclusivity)</td>
<td></td>
</tr>
<tr>
<td>☐ No changes</td>
<td></td>
</tr>
<tr>
<td>☑ New patent/exclusivity (Notify CDER OND IO)</td>
<td></td>
</tr>
<tr>
<td>❖ Finalize 55(b)(2) assessment</td>
<td>☐ Done</td>
</tr>
<tr>
<td>❖ For Breakthrough Therapy (BT) Designated drugs:</td>
<td>☑ Done</td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>☑ Done</td>
<td></td>
</tr>
<tr>
<td>❖ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td>☐ Done</td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or</td>
<td>☑ Done</td>
</tr>
<tr>
<td>secure email</td>
<td></td>
</tr>
<tr>
<td>❖ If an FDA communication will issue, notify Press Office of approval action after</td>
<td>☑ Done</td>
</tr>
<tr>
<td>confirming that applicant received courtesy copy of approval letter</td>
<td></td>
</tr>
<tr>
<td>❖ Ensure that proprietary name, if any, and established name are listed in the Application</td>
<td>☑ Done</td>
</tr>
<tr>
<td>Product Names section of DARRTS, and that the proprietary name is identified as the</td>
<td></td>
</tr>
<tr>
<td>“preferred” name</td>
<td></td>
</tr>
<tr>
<td>❖ Ensure Pediatric Record is accurate</td>
<td>☑ Done</td>
</tr>
<tr>
<td>❖ Send approval email within one business day to CDER-APPROVALS</td>
<td>☑ Done</td>
</tr>
<tr>
<td>❖ Take Action Package (if in paper) down to Document Room for scanning within two</td>
<td>☑ Done</td>
</tr>
<tr>
<td>business days</td>
<td></td>
</tr>
</tbody>
</table>
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/s/

ASHLEY S LUCCI VAUGHN
10/31/2017
Dear Yasameen,

Please refer to NDA 210259 acalabrutinib. We have the following additional edit to the label.

Under **Section 5.5 Atrial Fibrillation and Flutter** of the PI, please modify the last sentence, as follows: monitor for atrial fibrillation and atrial flutter and manage as appropriate.

Please send the revised label back in tracked changes via email to myself and Ashley by **12noon PM today**, October 30, 2017.

Once the team reviews and confirms the labeling is agreed upon, we will let you know so you can submit officially to the NDA file.

Kindly confirm receipt.

Thank you,
Theresa
The correction was made in the version submitted yesterday. Can you verify that it was received?

Thank you

Best regards,
Yasameen Qazen

From: LucciVaughn, Ashley <Ashley.LucciVaughn@fda.hhs.gov>
Sent: Thursday, October 26, 2017 7:43:58 AM
To: Yasameen Qazen
Cc: Carioti, Theresa
Subject: Sponsor Response Required: Fourth FDA USPI Review/ NDA 210259/ Acalabrutinib/ Acerta Pharma BV/ Response required via email by 12 PM EST Friday, October 27, 2017

Good Morning Yasameen,

Clinical has reviewed your request for the administrative change. They have requested you make the following correction and resubmit the label electronically to the NDA:

Cytopenias
Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE. [see Warnings and Precautions (5.3)].

Second Primary Malignancies
Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer. Advise patients to use sun protection [see Warnings and Precautions (5.4)].

Atrial Fibrillation and Flutter
Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions (5.5)].

Please confirm receipt.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993

Reference ID: 4173992
Dear Ashley

Please find attached our annotated and clean draft labels. All comments/revisions by the FDA have been accepted. Our only revision back is the administrative correction listed below. We will be submitting this to the NDA today. Please let me know when you have received it on your end.

Thank you so much for the speed in your replies.

Have a good evening.

Best Regards,

Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)...

Hi Yasameen,

I will send to the team for clearance of the administrative change and let you of their decisions, upon
Hello

We are in acceptance of all the changes made by the FDA. We will be making one administrative change to add a reference to the end of the cytopenias text for consistency with other items in section 17. See below. Please let me know if this is acceptable.

Cytopenias
Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE. [see Warnings and Precautions (5.4)].

Second Primary Malignancies
Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer. Advise patients to use sun protection [see Warnings and Precautions (5.4)].

Atrial Fibrillation and Flutter
Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions (5.5)].

Best Regards,
Yasameen Qazen
Dear Dr. Qazen,

Please refer to the attached *fourth* FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalabrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Friday October 27, 2017.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products

Reference ID: 4173992
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/s/

THERESA A CARIOTI
10/30/2017
Dear Dr. Qazen,

Our Safety team the PMR edits you submitted on October 18, 2017. Please refer to NDA 210259, PMR #3, listed below. It appears that the trial completion date and the final report submission date have been flipped, i.e. the trial will complete first, and the final report will be due after.

Please correct the dates, send your reply via email, and then submit the correction officially to the NDA file.

**PMR #3 Description:** Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of acalabrutinib in patients with 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.

**PMC Schedule Milestones:**
- Final Protocol Submission: June 2018
- Study/Trial Completion: December 2020
- Final Report Submission: July 2020

We request your response to the PMR document and submission to the NDA file by **12PM Monday October 30, 2017**.

Thank you,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4173989
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/s/

ASHLEY S LUCCI VAUGHN
10/30/2017
Dear Dr. Qazen,

Please refer to the attached fourth FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalabrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Friday October 27, 2017.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4172340
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/s/

ASHLEY S LUCCI VAUGHN
10/25/2017
Dear Dr. Qazen,

The Agency has accepted the agreed upon PMR edits you submitted on September 26, 2017. This communication contains the final PMR edits.

Please refer to NDA 210259, Acalabrutinib. 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 see attached a word version of the PMRs. If acceptable we ask you to submit both by email and officially to the NDA file, 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 or PMC designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR/PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH
THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

We request your response to the PMR document and submission to the NDA file by 12PM Monday October 23, 2017.

Thank you,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
10/18/2017
Dear Dr. Qazen,

Please refer to the attached third FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalabrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not “reject” the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Monday, October 23, 2017.

Please note: The label is still under review with our label review team in the Office of Prescription Drug Promotion. Comments from their team will not be available until Monday October 23, 2017, which at that time if there are any additional comments or recommendations they will be sent under separate communication.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4169216
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/s/

ASHLEY S LUCCI VAUGHN
10/18/2017
Hi Yasameen,

Yes you are correct, we will send a formal notification of acceptance of the PMR’s with the next labeling revisions, per the request of our CDTL.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Hello

Thank you for this timeline. It’s quite helpful. With regards to the PMRs, I thought the reviewers were ok with our minor edits. Should we expect more comments?

Best Regards,

Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)
Good Afternoon Yasameen,

The USPI redlines are adequate and currently under review. We should expect the next set of review revision next week along with the PMR feedback. The CDTL confirmed with me today that they anticipate next Thursday, after the next labeling meeting. We are also waiting for a labeling consult which will not be complete until the 23rd of October, so it is possible she will wait for their revisions as well. I will update you upon the completion of our labeling meeting next week.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Dear Ashley

Thank you for this. I also wanted to ask you if the redlines on the USPI are adequate and if can tell me when we could expect the next revision.

Thank you.

Best regards
Yasameen

On Oct 11, 2017, at 12:46 PM, LucciVaughn, Ashley <Ashley.LucciVaughn@fda.hhs.gov> wrote:
Good Afternoon Yasameen,

At this time, our review team have followed and noted that they do not have any further comments or requests for the container labels. The container revisions are acceptable.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

From: Yasameen Qazen [mailto:yasameen.qazen@acerta-pharma.com]
Sent: Tuesday, October 10, 2017 4:11 PM
To: LucciVaughn, Ashley
Cc: Carioti, Theresa
Subject: NDA 210259

Dear Ashley

The Acerta team is asking if there are further comments from the reviewer on the container labels?

Thank you.

Best regards,

Yasameen Qazen

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

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/s/

ASHLEY S LUCCI VAUGHN
10/13/2017
Good afternoon Yasameen,

I wanted to follow up with you regarding the ECG waveforms. They are still pending Agency review. Could you please advise the status of the upload in the ECG warehouse? We need to have this in order to complete our review by early next week in order to move forward with the review of your application. I have been notified from the review team that the Agency still does not have access to the waveforms.

End regards,

Ashley Lucci Vaughan, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

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Reference ID: 4165462
(b) (4)
(b) (4)
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(b) (4)
The response to the QT IR from Friday has been uploaded to the ECG warehouse tool. The information below has the identifier number for reference. We will respond with the same information in a cover letter tomorrow to the NDA. The upload is also linked to the NDA.

Please confirm receipt of this email.

Best Regards,

Yasameen Qazen
PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)

From: Yasameen Qazen
Sent: Friday, September 15, 2017 12:15 PM
To: LucciVaughn, Ashley <Ashley LucciVaughn@fda.hhs.gov>
Cc: Carioti, Theresa <Theresa Carioti@fda.hhs.gov>
Subject: RE: FDA-DHP/ QT Information request/ NDA 210259/Acalabrutinib/Acerta Pharma B V / Respond Required by 4 pm Tuesday September 19 2017

Dear Ashley,

I acknowledge receipt of this email request. Have a good weekend.

Best Regards,

Yasameen Qazen
PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)
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/s/

ASHLEY S LUCCI VAUGHN
10/10/2017
Dear Yasameen,

As a follow-up to your Late Cycle Meeting (LCM) held Friday September 29, 2017, regarding NDA 210259, I have provided a copy of the LCM Meeting Minutes.

A formal copy of the background package will also be sent via mail to the address provided in the NDA submission.

Please feel free to contact me if you have any questions.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
10/06/2017
Dear Dr. Qazen,

Please refer to the attached second FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalabrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Monday, October 16, 2017.

Please note that the patient information part of your labeling is still under review, and comment regarding the patient labeling will be sent under separate communication.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
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/s/

ASHLEY S LUCCI VAUGHN
10/06/2017
NDA 210259

INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Biopharmaceutics Response, Comments, and Requests:

1. FDA agrees with your proposal to revise the PSD specification limit to a \( D_{0.9,0.9} \) of NMT \( 0.45 \) \( \mu m \). However, PSD specification limits for \( D_{10} \) and \( D_{50} \) are needed; therefore, based on the measured API PSD used in the manufacture of the clinical and stability batches, submit a specification proposal for \( D_{10} \) and \( D_{50} \).

2. At this time of the review process, the proposed PBPK model is not acceptable because of the following:

   (a) Lack of demonstration of consistent relationship of predicted PSD used in GastroPlus model and measured PSD.
   (b) Over-parameterization (e.g., \( P_{eff} \), individual first-pass hepatic extraction ratios, without justification)
   (c) Insufficient validation (e.g., the validation is recommended to include those clinical trial data obtained from batches with different measured particle sizes)

Since the PBPK model is no longer a requirement to support the proposed particle size specification, we suggest that you withdraw the PBPK model from the NDA.
submission. We also suggest that after addressing our concerns, you re-submit the PBPK model under an Amendment to the IND. Note that an acceptable PBPK model will support widening of the PSD acceptance range.

FDA requests that you provide a response to the above requests by **Thursday, October 5, 2017**. However, if you like to further discuss our comments/requests; please schedule a teleconference with FDA.

If you have any questions, please contact me, at (240) 402-6153.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S
Good Afternoon Yasameen,

Per our phone discussion this afternoon, I contacted my clinical team regarding your submission of the carton label edits I have not received a response from them yet regarding if we could add that as a discussion point to tomorrows agenda. At this time I would advise if you have a specific question or wanted to request to move forward with printing at risk, respond via email and I can route to the team before tomorrow. They may be able to provide a response via email or on the call but there are no guarantees as they have not had a chance to complete their review of the edits.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
09/28/2017
Good Morning Yasameen,

At your earliest, could you please resubmit the labeling with the correct authorship of the comments. The label should contain our original comments with proper authorship as well as your comments/redlines/and acceptance.

To note, our comments are required to remain even after the Sponsor accepts the revisions, and separately add their comments in the document. I attached the original copy we sent you as well as the edited version you submitted for reference.

Please let me know if you have any questions.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Dear Ashley

Please find attached the annotated redline as well as a clean word version of the USPI for the review team. We look forward to discussing the comments by TC or by documented revisions back to us.

Thank you in advance. Please acknowledge receipt of this email and let me know if
you have any questions.

Best Regards,
Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)

From: LucciVaughn, Ashley [mailto:Ashley.LucciVaughn@fda.hhs.gov]
Sent: Tuesday, September 26, 2017 11:30 AM
To: Yasameen Qazen <yasameen.qazen@acerta-pharma.com>
Cc: Carioti, Theresa <Theresa.Carioti@fda.hhs.gov>
Subject: RE: NDA210259: USPI redline

Good Afternoon Yasameen,

The team confirmed that they would not have labeling discussions Friday, but will review your redlines/comments from the label and notify you if a T-con is needed based on the review of your responses.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

From: Yasameen Qazen [mailto:yasameen.qazen@acerta-pharma.com]
Sent: Tuesday, September 26, 2017 1:34 PM
To: LucciVaughn, Ashley
Cc: Carioti, Theresa
Subject: RE: NDA210259: USPI redline

Reference ID: 4159193
Dear Ashley

Thank you for your email. Based on our plan to have edits to you today, would it be acceptable to have label discussions as part of the agency for the LCM?

Best Regards,
Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)650-695-0086

From: LucciVaughn, Ashley [mailto:Ashley.LucciVaughn@fda.hhs.gov]
Sent: Tuesday, September 26, 2017 10:26 AM
To: Yasameen Qazen <yasameen.qazen@acerta-pharma.com>
Cc: Carioti, Theresa <Theresa.Carioti@fda.hhs.gov>
Subject: RE: NDA210259: USPI redline

Good Afternoon Yasameen,

You should receive the Late Cycle Meeting agenda by COB today. Regarding the T-con labeling discussion request, after meeting with the team yesterday our CDTL, feels it is too early for discussions as we have not completed the labeling review process or negotiations with Acerta. They would like to see your redlines with comments and provide responses once they have had time to review and discuss your comments/questions, internally. They have not approved a T-con pre-LCM, for these reasons.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4159193
Dear Ashley

Acerta is planning to send you a redline response and a clean version of the USPI today. Once you receive this, how soon do you feel we could schedule a TC with the review team to discuss the label? We are ok with meeting on Wed or Thursday, preferable Wednesday, but of course we are available at what works for you.

Also, will you be sending the agenda for the late cycle review meeting?

Best Regards,

Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o)650-695-0086
(m)
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/s/

----------------------------------------------------
ASHLEY S LUCCI VAUGHN
09/27/2017

Reference ID: 4159193
Dear Yasameen,

In preparation for your Late Cycle Meeting (LCM) scheduled Friday September 29, 2017, regarding NDA 210259, I have provided a copy of the LCM Background Package which outlines the agenda for Fridays meeting. Since the meeting has been scheduled as a teleconference, please provide dial-in information for the Agency to contact Acerta Pharma, during the scheduled meeting time.

A formal copy of the background package will also be sent via mail to the address provided in the NDA submission.

Please feel free to contact me if you have any questions.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
09/27/2017
Dear Dr. Qazen,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalbrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Friday, September 29, 2017.

Please note that the patient information part of your labeling is still under review, and comment regarding the patient labeling will be sent under separate communication.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

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

ASHLEY S LUCCI VAUGHN
09/25/2017
Dear Dr. Qazen,

For completeness, this communication contains the updated PMRs (inclusive of the email communication regarding the hepatic impairment PMR).

Please refer to NDA 210259, Acalabrutinib. 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 see attached a word version of the PMRs. Please insert dates and provide comments and edits as necessary, in clarifying mutually acceptable descriptions of the key trial elements.

Upon mutual agreement, we ask you to submit both by email and officially to the NDA file, 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 or PMC designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
a. For any new study to address a PMR/PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. *All protocol submissions are made to the IND.*

We request your response to the PMR document via email by **12PM Friday, September 29, 2017.** As the review continues, the Agency is working towards final agreement with the applicant on all PMRs by **October 16, 2017.**

Thank you,

Ashley Lucci Vaughn, MS  
Regulatory Health Project Manager  
Division of Hematology Products/Office of Hematology and Oncology Products  
10903 New Hampshire Avenue  
White Oak Bldg. 22 Rm. 2354  
Silver Spring, MD 20993  
Phone: 301-796-5718

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/s/

ASHLEY S LUCCI VAUGHN
09/25/2017
Dear Dr. Qazen,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalbrutinib.

Please review the FDA revised labeling with your team by:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Friday, September 29, 2017.

Please note that the patient information part of your labeling is still under review, and comment regarding the patient labeling will be sent under separate communication.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4156830
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/s/

ASHLEY S LUCCI VAUGHN
09/22/2017

Reference ID: 4156830
Good Afternoon Yasameen,

After review of your inquiry, clinical has determined that your request is acceptable to include the 90 day safety updated changes in redline in their responses to the label.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Hi Ashley

We noticed that the comments on this label are made on the original label submitted with the NDA. We also submitted an updated label with the 90 day safety update. When we respond we will add those changed in redline to reflect the updated data. Please let me know if that is acceptable.

Best Regards,

Yasameen Qazen
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Dear Dr. Qazen,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) for NDA 210259, acalbrutinib.

Please review the FDA revised labeling with your team by:
- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

After you have made any necessary changes to the PI, please send the revised tracked changes labeling documents via email to me before you make your official submission electronically. Any edits made must be in tracked changes.

Please provide your response via email by 12 PM EST Friday, September 29, 2017.

Please note that the patient information part of your labeling is still under review, and comment regarding the patient labeling will be sent under separate communication.

Please acknowledge receipt of this correspondence.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
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/s/

ASHLEY S LUCCI VAUGHN
09/22/2017

Reference ID: 4156943
NDA 210259

INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Drug Process:

1) In response for question #7 dated 8/25/17 you mentioned that Microbial limit testing method was validated using three lots of acalabrutinib capsules in accordance with USP<61> and <62>. Such report is not provided in the submission. Provide report supporting the claim.

2) We acknowledge you have submitted a Comparability Protocol that proposes alternative manufacturing sites at AstraZeneca, Sweden. [redacted] is also added as an additional stability testing site. You have stated in the Protocol that manufacturing procedures and testing procedures/specifications that will be approved in this NDA would be used at these sites. You also proposed that a CBE-30 be used for reporting on these additional manufacturing/testing facilities. The protocol states you will make three batches of drug product in the proposed facility but will provide only one batch of stability data for 3 months. This is not acceptable. You should provide stability data on all three batches in each packaging configuration [redacted]
If you have any questions, please contact me, at (240) 402-6153. Please respond by COB September 28, 2017.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 4 pm (ET) on Thursday, September 21, 2017, and followed with a formal submission to the NDA.

1. Please propose milestone timelines for the following post-marketing requirement (PMR).

   **PMR Description:**
   Conduct a clinical pharmacokinetic trial to determine an appropriate dose of acalabrutinib to minimize toxicity in patients with severe hepatic impairment. Design and conduct the trial 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.”

   **Final Protocol Submission:** Month/Year  
   **Trial Completion Date:** Month/Year  
   **Final Report Submission:** Month/Year

Kind Regards,

Ashley Lucci Vaughn, MS  
Regulatory Health Project Manager  
Division of Hematology Products/Office of Hematology and Oncology Products  
10903 New Hampshire Avenue  
White Oak Bldg. 22 Rm. 2354  
Silver Spring, MD 20993  
Phone: 301-796-5718

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/s/

ASHLEY S LUCCI VAUGHN
09/20/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm (ET) on Tuesday, September 26, 2017, and followed with a formal submission to the NDA.

Clinical Information Request:

1. The Agency requests additional information and clarification regarding patient 091-503-1502 whom were enrolled in study ACE-LY-004:
   a. Per the provided narrative in the CSR, this patient was reported to have died on Study day 32 as a result of disease progression. The patient also was reported to have a grade 4 AE of tumor lysis syndrome diagnosed on study day 29. The Agency seeks to clarify whether the patient’s death was due progressive disease or potentially due to tumor lysis syndrome associated with study therapy. We note the patient developed lymphocytosis starting on study day 8 and that the lymphocytosis was ongoing at the time of death. We also note that there are no radiographic assessments of disease after the initial screening studies in the provided data sets.
   b. Clarify the clinical or radiographic criteria that resulted in the determination of the cause of death as disease progression.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
09/19/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 4 pm (ET) on Tuesday, September 19, 2017, and followed with a formal submission to the NDA.

Division of Cardiovascular and Renal Products Information Request:

1. With regards to Study ACE‐HV‐005, please upload the digital ECGs with annotations to the ECG warehouse (www.ecgwarehouse.com).

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
09/15/2017
4.2 RECOMMENDATIONS FOR ACERTA PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. Carton Label:

1) Please replace the term “TRADENAME” with the conditionally acceptable proprietary name.

2) Relocate the net quantity statement (60 capsules) away from the product strength (100 mg), such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Draft Guidance: Container and Carton, April 2013 (lines 461-463).

3) As currently presented, there is no space allotted for the lot number and expiration. The lot number statement is required on the container and carton labeling when there is sufficient space per 21 CFR 201.10(l)(1). Please ensure the lot number is clearly differentiated from the expiration date. In addition, please ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.

4) As currently presented the NDC is denoted by a placeholder. Replace with NDC number and submit for Agency review.

5) Revise the storage information to add the temperature unit after each numerical temperature reading. For example, “Store at 20°C- 25°C (68°F-77°F); excursions permitted to 15°C - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

B. Container Labels (60 Capsules) and Professional Sample:

1) See A.1, A.4, and A.5.

C. Container Label (60 Capsules):

1) See A-3.
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/s/

ASHLEY S LUCCI VAUGHN
09/13/2017

Reference ID: 4152251
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

On Friday, September 1, 2017, your Mid-Cycle Meeting (via Teleconference) was held with the Agency regarding your application. The Mid-Cycle communication has been finalized and is attached for your records. The formal letter will be mailed to the address noted in your application.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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\(/s/\)

ASHLEY S LUCCI VAUGHN
09/07/2017

Reference ID: 4149784
INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Drug Substance:

1. Provide relevant characterization data and analytical validation data for the additional specified impurity [REDACTED] submitted in the quality response to information request on 8/30/2017.

If you have any questions, please contact me, at (240) 402-6153. Please respond by COB September 8, 2017.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S
NDA 210259

Acerta Pharma B.V.
Attention: Yasameen Qazen, PharmD
Director, Regulatory Science
2200 Bridge Parkway, Suite 101
Redwood City, CA 94065

Dear Dr. Qazen:

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

We also refer to the teleconference between representatives of your firm and the FDA on September 1, 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 Ashley Lucci Vaughn, Regulatory Project Manager at (301) 796-5718.

Sincerely,

{Tanya Wroblewski, MD
Acting 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: September 1, 2017; 9 am to 10 am EDT
Application Number: NDA 201259
Product Name: Acalabrutinib
Indication: Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Applicant Name: Acerta Pharma, B.V.
Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Beatrice Kallungal, MS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Acting Clinical Team Leader
Margaret Moreno, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Beatrice Kallungal, MS, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, PhD, Team Leader
Jingjing Ye, PhD, Reviewer

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Team Leader
Brenda Gehrke, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Team Leader
Vicky Hsu, PharmD, Reviewer
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

Clinical Pharmacology:
We will provide recommendations regarding drug-drug interactions in the labeling.
3.0 INFORMATION REQUESTS

CMC:
Drug Process:
The comparability protocol is inadequate. Provide stability data on three batches in each packaging configuration. Please update and resubmit CBE-30 proposal.

Drug Substance:
Provide relevant characterization data and analytical validation data for the additional specified impurity submitted in the quality response to information request on 8/30/2017.

Biopharmaceutics
The dissolution modeling data in support of the proposed acalabrutinib Particle Size Distribution ($D_{v,0.9}$) limit of $\mu$m are incomplete.

- Provide the in-house Microsoft Excel file/tool which was used to calculate dissolution rate based on Particle Size Distribution. Validate the Excel tool.
- No raw dissolution data from the internal Microsoft Excel tool file.
- Rationale for use of a gastric transit time of 50 hours in the model. Repeat the modeling using the appropriate gastric transit time and single dose records, if applicable.
- Rationale for using different Effective Permeability ($P_{eff}$) values in different individuals in the model. Justify this approach or modify the model as necessary.
- Provide a detailed sensitivity analysis report to support the excel file, “e17-002574-psd-justification-final-gastroplus-model-v5”.
- No model validation/verification.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no plan for risk evaluation and mitigation strategies (REMS).

5.0 ADVISORY COMMITTEE MEETING

At this time, there are no plans for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for September 29, 2017 at 9:00 AM EDT. We intend to send the briefing
package to you approximately 2 days in advance of the meeting. We plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by September 22, 2017. If these timelines change, we will communicate updates to you during the course of review.
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/s/

TANYA M WROBLEWSKI
09/07/2017
NDA 210259

INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Drug Substance:

1. The acceptance criterion of (b)(4)% for drug substance impurity (b)(4) is not adequately justified based on nonclinical qualification data or clinical studies. We recommend that you tighten the acceptance criteria for this impurity to at least (b)(4)% in drug substance release and stability specifications, and submit a revised specifications table.

2. The acceptance criterion of (b)(4)% for (b)(4) in the drug product appears to be wide; based on the toxicology batches the data support a specification up to (b)(4)% which equates to an impurity dose of (b)(4) mg/m(2) (b)(4). We recommend that the impurity be lowered to (b)(4)% . Provide a revised Drug Product (release/stability) specifications table.

If you have any questions, please contact me, at (240) 402-6153. Please respond by COB August 30, 2017.
Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S
Digitally signed by Rabiya Haider -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Haider -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2017.08.28 11:39:43 -04'00'
NDA 210259

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Acerta Pharma B.V.
c/o Acerta Pharma
2200 Bridge Parkway Suite 101
Redwood City, CA 94065

ATTENTION: Yasameen Qazen, PharmD
Director, Regulatory Science

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acalabrutinib Capsules, 100 mg.

We also refer to your correspondence, dated and received June 16, 2017, requesting review of your proposed proprietary name, Calquence.

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

If any of the proposed product characteristics as stated in your June 16, 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:


Reference ID: 4144475
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Ashley LucciVaughn, Regulatory Project Manager, in the Office of New Drugs at (301) 796-5718.

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
08/25/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm (ET) on Thursday, August 24, 2017, and followed with a formal submission to the NDA.

Clinical Pharmacology Information Request:

1. Clarify the percent contribution of each metabolic pathway to acalabrutinib’s overall metabolism, including percent contributions by individual CYP enzymes, GSH conjugation, and amide hydrolysis. Please also clarify hepatic and extra-hepatic metabolism of acalabrutinib.

2. Your DDI results with concomitant itraconazole showed that acalabrutinib AUC was increased by 5-fold whereas your hepatic impairment study showed a modest acalabrutinib AUC increases of ~50-65%. Please explain the apparent inconsistencies between the DDI and hepatic impairment study results given the metabolic pathways of acalabrutinib, which appears to be mostly hepatic. Please note that FDA does not agree with the exclusion of Subject 33008 in the normal hepatic function cohort.

3. Part 2 of your hepatic impairment trial was supposed to evaluate the effect of severe hepatic impairment on acalabrutinib PK. Please indicate whether the hepatic impairment study is still open and enrolling additional subjects. In addition, please share your proposal on how you intend to address dosing recommendation for patients with severe hepatic impairment.

Kind Regards,
Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
08/22/2017
INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Drug Substance:

1) In reference to the teleconference held with the Agency on 17-Aug-2017, provide the following:
   - Executed batch records for drug substance batches C665 and C666, when available. Provide data to demonstrate comparability between the C665 and C666 drug substance batches.
   - A summary of equipment differences and equipment qualification information for the (b)(4) and (b)(4) units used for the manufacture of C665 and C666 drug substance batches, respectively.

2) We note that five batches of drug substance are listed as manufactured at (b)(4). Clarify if these drug substance batches were manufactured at (b)(4). Additionally, clarify if the drug substance batches manufactured at AstraZeneca (b)(4). Provide additional details (b)(4) and a justification for any impact this step may have on drug substance quality.
3) Impurity is found at higher levels in AstraZeneca drug substance batches C657/1, C657/2, C657/3, C657/3H than in previously manufactured batches and in batches C665/1, C665/2, and C665/2H. Provide a justification for this increase in impurities. Clarify if drug substance batches C657/1, C657/2, C657/3, and C657/3H have been used in clinical studies, and provide the doses that were administered to patients.

4) Provide the reagents and solvents used for each step in the synthesis of starting materials and . Make note of any genotoxic impurities present in the starting material syntheses, and your control strategy for these impurities.

5) Provide the characterization data for specified drug substance impurities submitted in section 3.2.S.3.2 and for reference standards, including drug product impurities and .

6) Provide details for the steps that are used during manufacture of the drug substance. Clarify which manufacturing steps may be subject to operations and include adequate provisions for this.

7) Provide any updated stability data for the primary registration batches manufactured at , and the batches manufactured at AstraZeneca.

Drug Process/Micro:

1) It is stated on page 7 of the Manufacturing Process Development report within Module 3.2.P.2.3 that . There is however, no data provided to support such claims. Provide data supporting the claims.

2) Explain the upward trend observed in the assay for the Run 5 seen in data presented in Table 11 and Figure 17 (Manufacturing PD page 30). For better understanding, provide non-weight corrected data for the same table.

3) We acknowledge that you have performed . Please discuss if the study considered .
4) Please establish manufacturing hold time for each step and indicate in the batch manufacturing record. In order to justify any hold time of
(b)(4).

5) It is recommended you use theoretical capsule weight instead of “mean capsule weight”
(b)(4).

6) Provide (b)(4) specification and executed packaging batch data.

7) You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

   1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
   2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
   3. Describe activities taken when microbiological acceptance criteria are not met at control points.

   In addition to these points, address the following:
   1. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product. Test method suitability should be verified (if compendial methods are used) or validated.
   2. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.
   3. In the absence of historical data, you should perform microbial limits testing on stability batches according to the schedule provided in ICH Q1A section 2.2.6.

If you have any questions, please contact me, at (240) 402-6153. Please respond by **August 25, 2017**.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Good Afternoon Yasameen,

On Friday, September 1, 2017 from 10 am to 11 am EST, your Mid-Cycle Meeting (via Teleconference) has been scheduled with the Agency regarding your Application. At this meeting the following items are typically discussed with the Sponsor:

1. Significant review issues
2. Information request
3. Major safety concerns
4. Risk management updates
5. Proposed milestone dates

The meeting agenda will be communicated to you closer to the meeting date. At this time, please confirm your teams availability and provide a teleconference number to which the Agency may contact you during the scheduled meeting time.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
08/18/2017
NDA 210259

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acalabrutinib (ACP-196).

We also refer to your August 7, 2017, correspondence, received August 7, 2017 requesting a meeting to reach agreement on the proposed process validation approach and to enable early supply.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Rabiya Haider, Pharm.D., at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: A
Meeting Category: CMC Other

Meeting Date and Time: August 17, 2917 (11:00 am-12:00 pm) Est.
Meeting Location: Teleconference

Application Number: NDA 210259
Product Name: Acalabrutinib
Indication: Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Sponsor/Applicant Name: Acerta Pharma B.V.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 17, 2017, at the FDA, via teleconference between Acerta Pharma B.V. and the Office of Pharmaceutical Quality. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory business process manager (RBPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact Rabiya Laq, if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of meeting is to reach agreement on the proposed process validation approach and to enable early supply.

Preliminary comments are being sent to the sponsor August 16, 2017.
2.0 DISCUSSION

**Question 1:**
To ensure ibrutinib capsules are available for supply in line with a potential expedited NDA approval in Q4 2017, the Sponsor seeks FDA feedback on the proposed drug product validation plans outlined in the attached briefing document.

Does the Agency agree with the Sponsor’s proposed validation approach described in the briefing document?

**FDA Response to Question 1:**
Based on the information provided in the briefing packet, the proposed alternative process validation approach utilizing API from the C665 campaign and non-inked capsules appears to be acceptable.

Please note that the Agency does not approve process validation approaches. The Agency will assess the completed process validation studies during an onsite inspection.

**Question 2:**
Based on the priority review communication, NDA approval could occur as early as October 2017. The Sponsor has presented a supply option to meet this accelerated timeframe, using material from the product validation campaign, and would appreciate FDA feedback on the acceptability of this option.

Does the Agency agree with the Sponsor’s proposed supply option to meet a potential October 2017 approval?

**FDA Response to Question 2:**
It is our understanding, per your proposed alternate PPQ plan (Option 2), that the drug product capsules from the PPQ campaign will be used to support ongoing clinical programs and will use non-inked capsules. These capsules will not be suitable for commercial distribution. PPQ batches of capsules without an imprint are unacceptable for marketing because they would not meet CFR 206.10 and 206.7 requirements, and would not match the description on the approved labelling for commercial capsule.

It is our understanding that you propose to utilize the 3 drug product batches made with non-inked capsules for your PPQ study so that your first batch made with inked capsules can be commercially distributed in order to facilitate earlier access to patients. This proposed option appears adequate, subject to your successful completion of the drug product and drug substance PPQs prior to commercial distribution of product.

You indicated that this approach will allow for commercial product launch in November 2017. Please provide a more specific date in November on which you expect that the commercial product will be available.
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/s/

ANAMITRO BANERJEE
08/17/2017
NDA 210259

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acalabrutinib (ACP-196).

We also refer to the teleconference between representatives of your firm and the FDA on August 17, 2017. The purpose of the meeting was to reach agreement on the proposed process validation approach and to enable early supply.

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

If you have any questions, call Rabiya Haider, Pharm.D, Regulatory Business Process Manager at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes & Sponsor Slides
MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: CMC Other

Meeting Date and Time: August 17, 2917 (11:00 am-12:00 pm) Est.
Meeting Location: Teleconference

Application Number: NDA 210259
Product Name: Acalabrutinib
Indication: Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy

Sponsor/Applicant Name: Acerta Pharma B.V.

Meeting Chair: Anamitro Banerjee, Ph.D.
Meeting Recorder: Rabiya Haider, Pharm.D.

FDA ATTENDEES

Office of Pharmaceutical Quality
Anamitro Banerjee, Ph.D., ONDP/DNDP I/Branch II, Branch Chief (Acting)
Sherita McLamore-Hines, Ph.D., ONDP/DNDP I/Branch II, DHP Lead (Acting)
Paresma Patel, Ph.D., Drug Substance Reviewer
Rajiv Agarwal, Ph.D., Drug Product Reviewer
Quamrul Majumder, Ph.D., Drug Process Reviewer
Bogdan Kurtyka, Ph.D., OPF Team Lead (Acting)
Ruth Moore, Ph.D., Facilities Reviewer
Zhihao Peter Qiu, Facilities Branch Chief (Acting)
Rabiya Haider, Pharm.D., Regulatory Business Process Manager

Office of New Drugs
Tanya Wroblewski, M.D., Medical Team Lead
Albert Deisseroth, M.D., Ph.D., Assistant Division Director

SPONSOR ATTENDEES
Priti Patel, MD, Senior Medical Director, Clinical Development, Acerta Pharma
Jennifer Nicholson, MHA, Sr. Director., Global Regulatory Science Lead, Acerta Pharma
Yasameen Qazen, PharmD, Director., Regulatory Science, Acerta Pharma
Joseph Vu, MS, JD, Regulatory CMC, Acerta Pharma
Peter Carbonaro, MBA, Sr. VP, Manufacturing, Acerta Pharma
1.0 BACKGROUND

Purpose of meeting is to reach agreement on the proposed process validation approach and to enable early supply.

FDA sent Preliminary Comments to Acerta on August 16, 2017.

2. DISCUSSION

**Question 1:**
To ensure acalabrutinib capsules are available for supply in line with a potential expedited NDA approval in Q4 2017, the Sponsor seeks FDA feedback on the proposed drug product validation plans outlined in the attached briefing document.

Does the Agency agree with the Sponsor’s proposed validation approach described in the briefing document?

**FDA Response to Question 1:**
Based on the information provided in the briefing packet, the proposed alternative process validation approach utilizing API from the C665 campaign and non-inked capsules appears to be acceptable.

Please note that the Agency does not approve process validation approaches. The Agency will assess the completed process validation studies during an onsite inspection.

**Meeting Discussion:**
The sponsor accepted FDA’s response, no discussion occurred.

**Question 2:**
Based on the priority review communication, NDA approval could occur as early as October 2017. The Sponsor has presented a supply option to meet this accelerated timeframe, using material from the product validation campaign, and would appreciate FDA feedback on the acceptability of this option.

Does the Agency agree with the Sponsor’s proposed supply option to meet a potential October 2017 approval?

**FDA Response to Question 2:**
It is our understanding, per your proposed alternate PPQ plan (Option 2), that the drug product capsules from the PPQ campaign will be used to support ongoing clinical programs and will use non-inked capsules. These capsules will not be suitable for commercial distribution. PPQ batches of capsules without an imprint are unacceptable for marketing because they would not meet CFR 206.10 and 206.7 requirements, and would not match the description on the approved labelling for commercial capsule.

It is our understanding that you propose to utilize the 3 drug product batches made with non-inked capsules for your PPQ study so that your first batch made with inked capsules can be commercially distributed in order to facilitate earlier access to patients. This proposed option appears adequate, subject to your successful completion of the drug product and drug substance PPQs prior to commercial distribution of product.

You indicated that this approach will allow for commercial product launch in November 2017. Please provide a more specific date in November on which you expect that the commercial product will be available.

**Meeting Discussion:**
The applicant presented a new proposal to make one batch of the capsules in the PPQ campaign using API from the C665 campaign and inked capsules, to be released as commercial product. This proposal would result in availability of a limited supply by 13 October, 2017 to fill the gap until the commercial batches that use C666 API becomes available at the end of November, 2017.

FDA discussed with the applicant the possibility of advancing the date of availability of the first batch of commercial tablets that use API from the C666 campaign to earlier than November 30, 2017. Applicant informed FDA that they are continuously working to challenge the current timelines; however, the date of their reserved manufacturing slot at (the commercial drug product manufacturing site) is the main constraint to improving the currently projected timeline for the first commercial batch.

FDA proposed to the applicant that since the C665 API campaign is not considered material for commercial production (C665 being a clinical campaign), to use API from the C666 campaign to produce the single PPQ batch of inked-capsules for commercial supply. The applicant explained that was not feasible because manufacture for all 3 product PPQ batches was already underway. Therefore, the applicant will continue with the proposed product PPQ approach using C665 API. FDA will make a determination on the acceptability of the proposal to release the PPQ batch of inked capsules as commercial product following review of all applicable data and completion of the pre-approval inspection.

FDA will follow up the teleconference with an information request for C665 and C666 and executed batch records. The agency will also request a summary of equipment differences and equipment qualification for the and units used in the manufacture of C665 and C666 drug substance batches. FDA informed the applicant that the investigators would
expect to have access to the unit used for the C665 campaign during the upcoming inspection.

In response to the applicant’s inquiry regarding the decision on labeling and availability of the drug product for marketing on or before the action date; FDA indicated that the agency’s goal and expectation is that the labeling negotiations will be complete on time and product should be available soon after approval. The agency also indicated that the action letter would contain the PPQ batch number for commercial distribution if found acceptable.
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/s/

ANAMITRO BANERJEE
08/25/2017
From: LucciVaughn, Ashley  
To: “Yasameen Qazen”  
Cc: Carioti, Theresa  
Subject: FDA-DHP/ Clinical Pharmacology Information request/ NDA 210259/Acalabrutinib/Acerta Pharma B.V./ Respond Required by 12 pm Monday August 21 2017  
Date: Wednesday, August 16, 2017 9:38:00 AM

Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm (ET) on Monday, August 21, 2017, and followed with a formal submission to the NDA.

**Clinical Pharmacology Information Request:**

1) We note discrepancies between our calculations for AUC vs. your calculations for AUC in your Study Reports ACE-MY-001 and ACE-LY-003. Please check and confirm AUC calculations from all submitted Clinical Study Reports.

2) Please provide safety summary of patients with hepatic impairment (per NCI criteria) in each of your safety populations (ISS-LY004, ISS-100, ISS-ALL). Include incidences of SAEs, AEs leading to dose reduction, AEs leading to dose interruption/delay, AEs leading to drug discontinuation, and death by hepatic impairment category for each safety population.

Kind Regards,

Ashley Lucci Vaughn, MS  
Regulatory Health Project Manager  
Division of Hematology Products/Office of Hematology and Oncology Products  
10903 New Hampshire Avenue  
White Oak Bldg. 22 Rm. 2354  
Silver Spring, MD 20993  
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
08/16/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm (ET) on Monday, August 14, 2017, and followed with a formal submission to the NDA.

Clinical Pharmacology Information Request:

1. In your PBPK Report D8220C00003, you simulated 100 mg acalabrutinib BID with concomitant moderate CYP3A inhibitors (fluconazole, diltiazem, erythromycin). Please repeat the same analyses but simulate 100 mg acalabrutinib QD (instead of 100 mg acalabrutinib BID) with concomitant moderate CYP3A inhibitors. Present your data similar to the Tables 22-23 (effect of fluconazole), 26-27 (effect of diltiazem), 28-29 (effect of erythromycin), 34 (geometric mean values and ratios including P, M, P+M, P+M adjusted columns) in your PBPK Report D8220C00003. Please respond by 12 pm on Monday, August 14, 2017.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

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/s/

ASHLEY S LUCCI VAUGHN
08/11/2017
NDA 210259

MEETING REQUEST GRANTED

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acalabrutinib (ACP-196).

We also refer to your August 7, 2017, correspondence requesting a CMC meeting to reach agreement on the proposed process validation approach and to enable early supply. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: August 17, 2017
Time: 11:00 AM- 12:00 PM Eastern Standard Time
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

Invited CDER Participants: Rajiv Agarwal, Ph.D., Drug Product Reviewer
Quamrul Majumder, Ph.D., Drug Process Reviewer
Ruth Moore, Ph.D., Facilities Reviewer
Anamitro Banerjee, Ph.D., CMC Branch Chief (Acting)
Sherita McLamore-Hines, Ph.D., DHP Lead (Acting)
Rabiya Haider, Pharm.D., Sr. Regulatory Project Manager
Tanya Wroblewski, M.D., OND DHP Team Lead (Acting)

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

We acknowledge receipt of the meeting package included with the meeting request. If the materials presented in the meeting package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an

Reference ID: 4137959
email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Rabiya Haidar, Pharm.D.
Sr. Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
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/s/

RABIYA LAIQ
08/10/2017
INFORMATION REQUEST

Acerta Pharma B.V.
Attention: Yasameen Qazen, Pharm.D.
Director, Regulatory Science
2200 Bridge Parkway Ste 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196).

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

Please amend the NDA with newly generated drug product (inked and non-inked capsules) stability data.

If you have any questions, please contact me, at (240) 402-6153. Please respond by August 21, 2017.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S
Digitally signed by Rabiya Haider -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Haider -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2017.08.07 13:51:53 -04'00'
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm (ET) on Friday, August 11, 2017, and followed with a formal submission to the NDA.

Genomics Information Request:

1. Please submit analyses evaluating response to acalabrutinib in patients whose tumors have mutations that could predict resistance to BTK covalent inhibitors (e.g., BTK C481S), if available.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Reference ID: 4135107
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/s/

ASHLEY S LUCCI VAUGHN
08/04/2017
Thank you. I think it makes sense. I will let our team know. I guess we were sure if the goal date would change to Feb 1, but your explanation if fine for me.

Best regards,
Yasameen Qazen

Hi Dr. Qazen,

I am unsure if I understand your statement correctly, please let me know if this further calrifies:

The PDUFA goal date for filing (listed in the letter) is 60 days from the submission date (06/13/17) which would then be a filing date of 08/12/17, however we were able to process the submission earlier and have the letter to you by 08/01/17 so we exceeded the PDUFA goal date by filing earlier than the 08/12/17, timeline. In that case we would till act on the priority application within 6 months of the PDUFA filing date (08/12/17) . The dates in the letter still apply.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
Sorry to bother you but then is the PDUFA goal date based on the filing date of Aug 1 or the FDA internal goal 60 day filing date of Aug 12? I realize it's a goal but wanted to confirm since the Agency performance goals state that: review and act on 90 percent of priority NME NDA and original BLA submissions within 6 months of the 60 day filing date.

Thank you in advance for your response

Best regards,
Yasameen Qazen

---

From: LucciVaughn, Ashley <Ashley.LucciVaughn@fda.hhs.gov>
Sent: Thursday, August 3, 2017 7:08:45 AM
To: Yasameen Qazen
Cc: Carioti, Theresa
Subject: RE: NDA 210259-Application Filed_No Filing Issues/Acalabrutinib/Acerta Pharma B.V.

Good Morning Dr. Qazen

The filed date is August 01, 2017, the date you received your letter. August 12th was our regulatory goal date to have had the letter to you.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

---

From: Yasameen Qazen [mailto:yasameen.qazen@acerta-pharma.com]
Sent: Tuesday, August 01, 2017 5:22 PM
To: LucciVaughn, Ashley
Cc: Carioti, Theresa
Subject: Re: NDA 210259-Application Filed_No Filing Issues/Acalabrutinib/Acerta Pharma B.V.

Hi

I have a question: is the NDA filed as of today or as of 60 days from the submission date of June 13, meaning Aug 12? This critical for our company press release so I would appreciate the clarification.
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

The Division of Hematology has completed their initial review of your submission and has determined your application is sufficiently complete to permit a substantive review. No filing issues have been identified. In accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The application will undergo Priority review, with a user fee goal date of February 13, 2018.

If you have any question, please do not hesitate to contact me.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

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Reference ID: 4134651
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/s/

ASHLEY S LUCCI VAUGHN
08/03/2017
NDA 210259

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Acerta Pharma B.V.
Attention: Yasameen Qazen, PharmD
Director, Regulatory Science
2200 Bridge Parkway, Suite 101
Redwood City, CA  94065

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) dated June 13, 2017, received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for acalabrutinib capsule, 100 mg.

We also refer to your amendments dated June 22 and July 13 (2), 27, and 31, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is February 13, 2018. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm).

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

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by
September 22, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is August 18, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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](PLRRequirementsPrescribingInformation) and [PLLR Requirements for Prescribing Information](PLLRRequirementsPrescribingInformation) 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.

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**

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

Reference ID: 4133390
OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

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

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

**REQUIRED PEDIATRIC ASSESSMENTS**

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

If you have any questions, call Ashley Lucci Vaughn, Regulatory Project Manager, at (301) 796-5718.

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/

ANN T FARRELL
08/01/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

The Division of Hematology has completed their initial review of your submission and has determined your application is sufficiently complete to permit a substantive review. No filing issues have been identified. In accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The application will undergo Priority review, with a user fee goal date of February 13, 2018.

If you have any question, please do not hesitate to contact me.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
08/01/2017
Dear Dr. Donaldson:


We also refer to your June 6, 2017, request for Breakthrough Therapy designation. We have reviewed your request and have determined that acalabrutinib (ACP-196) for the treatment of patients with mantle cell lymphoma (MCL) that have received at least one prior therapy, meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of acalabrutinib (ACP-196) for the treatment of patients with mantle cell lymphoma (MCL) that have received at least one prior therapy, to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.¹

When Breakthrough Therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics, Attachment 1, for potential topics for

discussion at this initial Breakthrough Therapy meeting.

We note your recent New Drug Application, NDA 210259, submitted on June 13, 2017. At this point in your drug development program, holding this initial Breakthrough Therapy meeting is not necessary. However, you may contact the Regulatory Project Manager noted below to determine if any other information is required at this time to expedite the review of your breakthrough designated product.

If you have any questions, call Ashley Lucci Vaughn, Regulatory Project Manager, at (301) 796-5718.

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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2

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/s/

ANN T FARRELL
07/31/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Response required to the information request, below, via email by 12 pm am (ET) on Wednesday, August 9, 2017, and followed with a formal submission to the NDA.

Stats Information Request:

Provide the executable programming codes that you used to derive and analyze ORR (including CR) and DOR, by INV and IRC, per Lugano and Cheson criteria for the pivotal study ACE-LY-004. Your programming codes will greatly speed up our review because preparing programs to derive ORR and DOR from raw data will take reviewers a lot of time due to the complexities.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
07/31/2017
## CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
<th>IND 118717</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>June 6, 2017</td>
</tr>
<tr>
<td>Product</td>
<td>Acalabrutinib</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Acerta Pharma B.V.</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>OHOP/DHP</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>August 6, 2017</td>
</tr>
</tbody>
</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

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

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

   Proposed Indication: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

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

   *If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:*

3. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening?
      - [ ] YES  
      - [x] NO

      *If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:*

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      - [x] YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - [ ] Undetermined
      - [ ] NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

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Reference ID: 4131467
i. Only animal/nonclinical data submitted as evidence
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\) historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off  (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

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

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

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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

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

**Brief Description of the Drug**

Acalabrutinib is a second generation, orally available inhibitor of Bruton’s Tyrosine Kinase (BTK). Acalabrutinib selectively and irreversibly binds to BTK, which plays a critical role in the B-cell receptor (BCR) signaling pathway. Acalabrutinib and its active metabolite irreversible bind to a cysteine residue in the BTK active site resulting in inactivation. The 50% inhibitory concentration (IC\(_{50}\)) of acalabrutinib is \(\leq 5nM\). Acalabrutinib has demonstrated selective inhibition of BTK, with inhibition of only two other kinases, bone marrow kinase on X chromosome (BMX) and erb-b2 receptor tyrosine kinase (ERBB4). Acalabrutinib at a dose of 100mg BID provided near complete BTK occupancy over 24 hours at steady state in patients with Chronic Lymphocytic Leukemia(PLL) and was chosen as the dose to further investigate in patients with mantle cell lymphoma. Acalabrutinib is currently not approved for any indication.

**Brief Description of the Disease and intended population**

Mantle cell lymphoma is a serious and life threatening condition with median overall survival of 3-5 years. Mantle Cell lymphoma is a rare subtype of Non-Hodgkin lymphoma (NHL) with a poor prognosis, generally considered incurable with current available therapies. The disease typically affects men with a median age at diagnosis of 64 and occurs in 3000-4000 Americans per year. Mantle cell lymphoma is characterized by the chromosomal translocation t(11;14) with results in constitutive activation of anti-apoptotic pathways.

Treatment of newly diagnosed patients is typically multi-agent chemotherapy regimens (R-CHOP or Hyper-CVAD)\(^1\) and in patients who are eligible, subsequent autologous stem cell transplantation followed by rituximab maintenance therapy. While the majority of patients attain a CR the response is not durable and most patients will eventually relapse. For patients with relapsed and refractory disease, the median overall survival is 1-2 years.\(^2\)

There is no accepted standard of care for patients with relapsed or refractory disease. Therapeutic options include salvage chemotherapy regimens and targeted therapies, but complete response rates are low (\(< 30\%\)) with very short duration of responses. Bortezomib and lenalidamide are the only approved (regular) treatments for relapsed and refractory MCL and are associated with overall response rate (ORRs) of 31\% and 25\%, respectively. Ibrutinib (a first generation BTK inhibitor) received accelerated approval in 2013 for relapsed and refractory mantle cell lymphoma based on an ORR of 66\% and a confirmatory trial is ongoing with results expected in 2018-19. The intended population for acalabrutinib is patients with relapsed or refractory mantle cell lymphoma who have failed at least 1 prior therapy.

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

   a. **Endpoints considered by the sponsor as supporting the BTDR:**

   - Overall response rate (ORR) defined as the percentage of patients as assessed by the investigator achieving a partial response (PR) or complete response (CR) according to the currently accepted Lugano classification of NHL\(^3\). Secondary endpoints are investigator-assessed duration of response (DOR), progression free survival (PFS), overall survival (OS), and independent review committee (IRC)-assessed ORR, DOR and PFS by Cheson criteria.

   b. **Endpoints(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.**

   - Overall response rate (complete and partial response) and duration of response.

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

     None

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

Bortezomib and Lenalidomide are considered available therapy for patients with relapsed or refractory mantle cell lymphoma although there is no accepted standard of care therapy for this group of patients. Table 1 describes the available therapy and response rates for patients with relapsed or refractory mantle cell lymphoma.

Table 1: Available Therapies for Relapsed or Refractory Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>ORR (95% CI)</th>
<th>CR</th>
<th>Median DOR, mo</th>
<th>Response Criteria used</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (N=155)</td>
<td>31% (24,39)</td>
<td>8%</td>
<td>9.3</td>
<td>Cheson 1999</td>
<td>Regular Approval</td>
</tr>
<tr>
<td>Lenalidomide (N=133)</td>
<td>26% (10,34)</td>
<td>7%</td>
<td>16.6</td>
<td>Cheson 1999</td>
<td>Regular Approval</td>
</tr>
<tr>
<td>Ibrutinib (N=111)</td>
<td>68% (56,75)</td>
<td>22%</td>
<td>17.5</td>
<td>Cheson 2007</td>
<td>Accelerated Approval</td>
</tr>
</tbody>
</table>

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

Ibrutinib is a 1st in class Bruton’s tyrosine kinase inhibitor that was granted breakthrough designation for patients with relapsed or refractory mantle cell in 2013 (ORR 68%, 95% CI 56,75). The Sponsor is conducting a randomized phase 3 trial in newly diagnosed mantle cell lymphoma which will serve as the confirmatory trial and final results are expected in 2018-19. Ibrutinib received approval(regular) for several other hematologic conditions: chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, CLL with 17p deletion, and Waldenstrom’s macroglobulinemia

Ibrutinib differs from acalabrutinib in that it is a less selective inhibitor and the binding site is different.

10. Information related to the preliminary clinical evidence:

The Sponsor submitted one clinical trial to support this breakthrough therapy designation request. Trial ACE-LY-004 is a phase II, single arm, open-label, multicenter, global study evaluating acalabrutinib as monotherapy in patients with relapsed and refractory mantle cell lymphoma. The study enrolled 124 patients who had received at least one but not more than five prior therapies. Patients received 100mg of acalabrutinib as monotherapy daily until progression or unacceptable drug-related toxicity.

The primary efficacy endpoint is overall response rate defined as CR or PR per the 2014 Lugano classification criteria as assessed by investigator. Secondary endpoints included duration of response, The study completed enrollment in February of 2016 and reported response status with duration of response data for at least 12 months in responders.

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

Reference ID: 4131467
Table 2: Demographics for Study ACE-LY-004

<table>
<thead>
<tr>
<th>ACE-LY-004 Demographics N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male n (%)</td>
</tr>
<tr>
<td>Ann Arbor Staging for lymphoma, n(%)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>ECOG Performance Status n (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Number of Prior Regimens</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>&gt; 3</td>
</tr>
<tr>
<td>Refractory Disease at Baseline</td>
</tr>
<tr>
<td>Yes (%)</td>
</tr>
</tbody>
</table>

Table 3: Study ACE-LY-004 Efficacy Results

<table>
<thead>
<tr>
<th>Overall Response and Duration of Response by Investigator per Lugano 2014</th>
<th>Acalabrutinib (N = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(%) 95% CI</td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate(ORR)</td>
<td></td>
</tr>
<tr>
<td>Complete Response(CR)</td>
<td>100 (80.6) (72,87)</td>
</tr>
<tr>
<td>Partial Response(PR)</td>
<td>49 (39.5) (31,49)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>51 (41.1) (32,50)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (8.9) (3,13)</td>
</tr>
<tr>
<td>Duration of Response(DOR)(months), median(95% CI)</td>
<td>NR (13.5, NR)</td>
</tr>
<tr>
<td>12-month DOR estimate, % 95% CI</td>
<td>72% (62,80)</td>
</tr>
<tr>
<td>18-month DOR estimate, % 95% CI</td>
<td>63% (49,74)</td>
</tr>
<tr>
<td>Follow-up,(months), median(range)</td>
<td>15.2 (0.3,23.7)</td>
</tr>
</tbody>
</table>

Figure1. Duration of Response in Subjects who Achieved a CR or PR in Study ACE-LY-004
b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.

The overall response rate of acalabrutinib can be considered preliminary clinical evidence of substantial improvement over available therapies. The ORR of 80.6% is ~2 fold higher than available therapies of bortezomib and lenalidomide. The CR rate of 40% is 2 fold higher than ibrutinib and 3-5 fold higher than bortezomib and lenalidomide.

Table 4. Response Rates in Available Therapy compared to Acalabrutinib

<table>
<thead>
<tr>
<th></th>
<th>Acalabrutinib N = 124</th>
<th>Ibrutinib* N = 111</th>
<th>Bortezomib N = 155</th>
<th>Lenalidomide N = 134</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate (ORR) %, 95% CI</strong></td>
<td><strong>80.6 (72.6, 87.2)</strong></td>
<td><strong>66 (56.2, 74.5)</strong></td>
<td><strong>31 (24,39)</strong></td>
<td><strong>26 (18,34)</strong></td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td><strong>40 (31,49)</strong></td>
<td><strong>17 (NR)</strong></td>
<td><strong>8 (4,13)</strong></td>
<td><strong>7 (NR)</strong></td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td><strong>41(32,50)</strong></td>
<td><strong>49(NR)</strong></td>
<td><strong>23(17,31)</strong></td>
<td><strong>19 (NR)</strong></td>
</tr>
<tr>
<td><strong>Duration of response (months)</strong></td>
<td><strong>NR (13.5, NR)</strong></td>
<td><strong>17.5 (15.8, NR)</strong></td>
<td><strong>9.3 (5.4, 13.8)</strong></td>
<td><strong>16.6 (7.7, 26.7)</strong></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
During an EOP2 meeting in March 2016, the sponsor was asked to provide data on at least 12 month DOR for all responders. This data was provided and demonstrated that 72% of responders remained in response at 12 months.

- **Safety data:**

  The safety of acalabrutinib has been evaluated in over 610 patients who have taken acalabrutinib at doses between 100mg daily to 400mg daily including 124 patients who received acalabrutinib at a dose of 100mg BID as part of the pivotal study in support of the BTDR and recently submitted NDA. The median duration of treatment for the group of patient with mantle cell lymphoma was 13.8 months. The most frequently reported grade 3 or 4 AEs were neutropenia (10.5%) and anemia (8.9%). Serious Adverse Events (SAEs) were reported in 38.7% of the subjects. In study ACE-LY-004, 5.6% of patients discontinued treatment due to an adverse event. An integrated safety analysis of the 610 patients who have been exposed to acalabrutinib AEs leading to dose delay, dose reduction and treatment discontinuation were reported at 33.4%, 6.1% and 2.5% respectively. Preliminary safety profile appears comparable to first generation BTK inhibitor.

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

   - **GRANT**: Grant Breakthrough Designation for the treatment of patients with Mantle Cell Lymphoma who have received at least one prior therapy.

   Rationale: Relapsed and refractory mantle cell therapy is a serious and life threatening disease and substantial clinical evidence demonstrated and overall response rate of 80% (95% CI: 72.87) with median duration of response that is not estimable (median follow-up for DOR of 15 months). The 12-month estimate of duration of response in responders is 72%. The demonstration of a 80% response rate is higher than currently available therapy and is clinically meaningful in a population for which no standard approach to 2nd line therapy or beyond has been established. This response is supported by the complete response rate of 40% which is ~2-4 fold higher than available therapies.

   *Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

   - **DENY:**

     Provide brief summary of rationale for denial:

     *Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

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

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

   The Sponsor submitted NDA on June 13, 2017 for proposed indication in patients with Mantle Cell Lymphoma. The Sponsor has initiated a potential confirmatory trial, ACE-LY-308, a phase 3 randomized trial comparing bendamustine and Rituxan versus bendamustine +
rituximab + acalabrutinib in newly diagnosed patients with mantle cell lymphoma. The primary endpoint is progression free survival (PFS). The Sponsor also has several ongoing trials in other hematologic malignancies (CLL, NHL).

The Division is currently reviewing the submitted NDA under an expedited review timeframe with consideration for an accelerated approval. The Division held a pre-NDA meeting on June 2, 2017 with the objective to reach agreement on the proposed NDA with regards to efficacy and safety data, PK modelling, a 90 day safety update, and data submission. The Division and Sponsor have also had previous meetings to discuss and agree upon the design of the ongoing Phase 3 trial that could potentially serve as confirmatory study.

13. List references, if any:


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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

Reference ID: 4131467
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
MARGRET E MERINO
07/28/2017

TANYA M WROBLEWSKI
07/28/2017

ANN T FARRELL
07/28/2017

Reference ID: 4131467
Dear Dr. Qazen,

In regards to the In Silico model development on pharmaceutical development (API particle size specification) for the NDA above, the CMC team in unable to locate raw modeling data in your application. Please submit this modeling data to the NDA or direct us to where it is located in your submission.

We request a response by July 31, 2017.

Please confirm receipt of this email.

Regards,

*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
As the Council agrees with DHP’s recommendation to grant Acerta Pharma B.V.’s breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the July 26, 2017 meeting agenda.

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

Hi! OMP has scheduled a Medical Policy Council discussion on July 26, 2017 regarding the breakthrough therapy designation request from Acerta Pharma B.V. for its IND 118717, Acalabrutinib, for the treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy.

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

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

Would you please review DHP’s recommendation and let me know by COB Friday, July 21 if –

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

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

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

Kayla Garvin
Project Manager
CDER/Office of Medical Policy

WO51/6314
301-796-7578
CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
<th>IND 118717</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>June 6, 2017</td>
</tr>
<tr>
<td>Product</td>
<td>Acalabrutinib</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Acerta Pharma B.V.</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>OHOP/DHP</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>August 6, 2017</td>
</tr>
</tbody>
</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

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

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):
   
   Proposed Indication: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

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

   If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

3. Consideration of Breakthrough Therapy Criteria:
   a. Is the condition serious/life-threatening?  
      □ YES  □ NO

   If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?  
      □ YES the BTDR is adequate and sufficiently complete to permit a substantive review  
      □ Undetermined  
      □ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

---

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)

v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\)/historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

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

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

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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

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

**Brief Description of the Drug**

Acalabrutinib is a second generation, orally available inhibitor of Bruton’s Tyrosine Kinase (BTK). Acalabrutinib selectively and irreversibly binds to BTK, which plays a critical role in the B-cell receptor (BCR) signaling pathway. Acalabrutinib and its active metabolite irreversible bind to a cysteine residue in the BTK active site resulting in inactivation. The 50% inhibitory concentration (IC\(_{50}\)) of acalabrutinib is \(\leq 5\)nM. Acalabrutinib has demonstrated selective inhibition of BTK, with inhibition of only two other kinases, bone marrow kinase on X chromosome (BMX) and erb-b2 receptor tyrosine kinase (ERBB4). Acalabrutinib at a dose of 100mg BID provided near complete BTK occupancy over 24 hours at steady state in patients with Chronic Lymphocytic Leukemia(CLL) and was chosen as the dose to further investigate in patients with mantle cell lymphoma. Acalabrutinib is currently not approved for any indication.

**Brief Description of the Disease and intended population**

Mantle cell lymphoma is a serious and life threatening condition with median overall survival of 3-5 years. Mantle Cell lymphoma is a rare subtype of Non-Hodgkin lymphoma (NHL) with a poor prognosis, generally considered incurable with current available therapies. The disease typically affects men with a median age at diagnosis of 64 and occurs in 3000-4000 Americans per year. Mantle cell lymphoma is characterized by the chromosomal translocation t(11;14) with results in constitutive activation of anti-apoptotic pathways.

Treatment of newly diagnosed patients is typically multi-agent chemotherapy regimens (R-CHOP or Hyper-CVAD) and in patients who are eligible, subsequent autologous stem cell transplantation followed by rituximab maintenance therapy. While the majority of patients attain a CR the response is not durable and most patients will eventually relapse. For patients with relapsed and refractory disease, the median overall survival is 1-2 years.

There is no accepted standard of care for patients with relapsed or refractory disease. Therapeutic options include salvage chemotherapy regimens and targeted therapies, but complete response rates are low (< 30%) with very short duration of responses. Bortezomib and lenalidamide are the only approved (regular) treatments for relapsed and refractory MCL and are associated with overall response rate (ORRs) of 31% and 25%, respectively. Ibrutinib (a first generation BTK inhibitor) received accelerated approval in 2013 for relapsed and refractory mantle cell lymphoma based on an ORR of 66% and a confirmatory trial is ongoing with results expected in 2018-19. The intended population for acalabrutinib is patients with relapsed or refractory mantle cell lymphoma who have failed at least 1 prior therapy.

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

   a. **Endpoints considered by the sponsor as supporting the BTDR:**

      • Overall response rate (ORR) defined as the percentage of patients as assessed by the investigator achieving a partial response (PR) or complete response (CR) according to the currently accepted Lugano classification of NHL. Secondary endpoints are investigator-assessed duration of response (DOR), progression free survival (PFS), overall survival (OS), and independent review committee (IRC)-assessed ORR, DOR and PFS by Cheson criteria.

   b. **Endpoints(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.**

      • Overall response rate (complete and partial response) and duration of response.

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

      None

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

Bortezomib and Lenalidomide are considered available therapy for patients with relapsed or refractory mantle cell lymphoma although there is no accepted standard of care therapy for this group of patients. Table 1 describes the available therapy and response rates for patients with relapsed or refractory mantle cell lymphoma.

Table 1: Available Therapies for Relapsed or Refractory Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ORR (95% CI)</th>
<th>CR</th>
<th>Median DOR, mo</th>
<th>Response Criteria used</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (N=155)</td>
<td>31% (24,39)</td>
<td>8%</td>
<td>9.3</td>
<td>Cheson 1999&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Regular Approval</td>
</tr>
<tr>
<td>Lenalidomide (N=133)</td>
<td>26% (10,34)</td>
<td>7%</td>
<td>16.6</td>
<td>Cheson 1999&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Regular Approval</td>
</tr>
<tr>
<td>Ibrutinib (N=111)</td>
<td>68% (56,75)</td>
<td>22%</td>
<td>17.5</td>
<td>Cheson 2007&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Accelerated Approval</td>
</tr>
</tbody>
</table>

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.

Ibrutinib is a 1<sup>st</sup> in class Bruton’s tyrosine kinase inhibitor that was granted breakthrough designation for patients with relapsed or refractory mantle cell lymphoma in 2013 (ORR 68%, 95% CI 56,75). The Sponsor is conducting a randomized phase 3 trial in newly diagnosed mantle cell lymphoma which will serve as the confirmatory trial and final results are expected in 2018-19. Ibrutinib received approval(regular) for several other hematologic conditions: chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, CLL with 17p deletion, and Waldenstrom’s macroglobulinemia

Ibrutinib differs from acalabrutinib in that it is a less selective inhibitor and the binding site is different.

10. Information related to the preliminary clinical evidence:

The Sponsor submitted one clinical trial to support this breakthrough therapy designation request. Trial ACE-LY-004 is a phase II, single arm, open-label, multicenter, global study evaluating acalabrutinib as monotherapy in patients with relapsed and refractory mantle cell lymphoma. The study enrolled 124 patients who had received at least one but not more than five prior therapies. Patients received 100mg of acalabrutinib as monotherapy daily until progression or unacceptable drug-related toxicity.

The primary efficacy endpoint is overall response rate defined as CR or PR per the 2014 Lugano classification criteria as assessed by investigator. Secondary endpoints included duration of response, The study completed enrollment in February of 2016 and reported response status with duration of response data for at least 12 months in responders.

<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
Table 2: Demographics for Study ACE-LY-004

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median (range)</th>
<th>68 (42,90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male n (%)</td>
<td>99 (79.8)</td>
</tr>
<tr>
<td>Ann Arbor Staging for lymphoma, n(%)</td>
<td>I 2 (1.6)</td>
<td>II 7 (5.6)</td>
</tr>
<tr>
<td>ECOG Performance Status n (%)</td>
<td>0 71 (57.3)</td>
<td>1 44 (35.3)</td>
</tr>
<tr>
<td>Number of Prior Regimens</td>
<td>Median (range)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Refractory Disease at Baseline</td>
<td>Yes (%)</td>
<td>30 (24.2)</td>
</tr>
</tbody>
</table>

Table 3: Study ACE-LY-004 Efficacy Results

<table>
<thead>
<tr>
<th>Overall Response and Duration of Response by Investigator per Lugano 2014</th>
<th>Acalabrutinib (N = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate(ORR)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Complete Response(CR)</td>
<td>100 (80.6)</td>
</tr>
<tr>
<td>Partial Response(PR)</td>
<td>49 (39.5)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>51 (41.1)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (8.9)</td>
</tr>
<tr>
<td></td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Duration of Response(DOR)(months), median(95% CI)</td>
<td>NR (13.5, NR)</td>
</tr>
<tr>
<td>12-month DOR estimate, % (95% CI)</td>
<td>72% (62.80)</td>
</tr>
<tr>
<td>18-month DOR estimate, % (95% CI)</td>
<td>63 (49.74)</td>
</tr>
<tr>
<td>Follow-up(months), median(range)</td>
<td>15.2 (0.3, 23.7)</td>
</tr>
</tbody>
</table>
b. Include any additional relevant information. Consider the following in your response:

- **Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.**

The overall response rate of acalabrutinib can be considered preliminary clinical evidence of substantial improvement over available therapies. The ORR of 80.6% is ~2 fold higher than available therapies of bortezomib and lenalidomide. The CR rate of 40% is 2 fold higher than ibrutinib and 3-5 fold higher than bortezomib and lenalidomide.

Table 4. Response Rates in Available Therapy compared to Acalabrutinib

<table>
<thead>
<tr>
<th>MCL</th>
<th>Acalabrutinib N = 124</th>
<th>Ibrutinib* N = 111</th>
<th>Bortezomib N = 155</th>
<th>Lenalidomide N = 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate (ORR) %, 95% CI</td>
<td>80.6 (72.6, 87.2)</td>
<td>66 (56.2, 74.5)</td>
<td>31 (24,39)</td>
<td>26 (18,34)</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>40 (31,49)</td>
<td>17 (NR)</td>
<td>8 (4,13)</td>
<td>7 (NR)</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>41(32,50)</td>
<td>49(NR)</td>
<td>23(17,31)</td>
<td>19 (NR)</td>
</tr>
<tr>
<td>Duration of response (months) Median (95% CI)</td>
<td>NR (13.5, NR)</td>
<td>17.5 (15.8, NR)</td>
<td>9.3 (5.4, 13.8)</td>
<td>16.6 (7.7, 26.7)</td>
</tr>
</tbody>
</table>
Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.

During an EOP2 meeting in March 2016, the sponsor was asked to provide data on at least 12 month DOR for all responders. This data was provided and demonstrated that 72% of responders remained in response at 12 months.

Safety data:

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- GRANT: Grant Breakthrough Designation for treatment of patients with Mantle Cell Lymphoma who have received at least one prior therapy.

Rationale: Relapsed and refractory mantle cell therapy is a serious and life threatening disease and substantial clinical evidence demonstrated and overall response rate of 80% (95% CI: 72,87) with median duration of response that is not estimable (median follow-up for DOR of 15 months). The 12-month estimate of duration of response in responders is 72%. The demonstration of a 80% response rate is higher than currently available therapy and is clinically meaningful in a population for which no standard approach to 2nd line therapy or beyond has been established. This response is supported by the complete response rate of 40% which is ~2-4 fold higher than available therapies.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

- DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

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

Reference ID: 4128797
The Sponsor submitted NDA on June 13, 2017 for proposed indication in patients with Mantle Cell Lymphoma. The Sponsor has initiated a potential confirmatory trial, ACE-LY-308, a phase 3 randomized trial comparing bendamustine and Rituxan versus bendamustine + rituximab+ acalabrutinib in newly diagnosed patients with mantle cell lymphoma. The primary endpoint is progression free survival (PFS). The Sponsor also has several ongoing trials in other hematologic malignancies (CLL, NHL).

The Division is currently reviewing the submitted NDA under an expedited review timeframe with consideration for an accelerated approval. The Division held a pre-NDA meeting on June 2, 2017 with the objective to reach agreement on the proposed NDA with regards to efficacy and safety data, PK modelling, a 90 day safety update, and data submission. The Division and Sponsor have also had previous meetings to discuss and agree upon the design of the ongoing Phase 3 trial that could potentially serve as confirmatory study.

13. List references, if any:


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

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

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}
Breakthrough Therapy Designation
IND 118717
Acalabrutinib

Proposed Indication: Treatment of patients with Mantle Cell Lymphoma who have received at least one prior therapy

Margret Merino, MD
Division of Hematology Products
Office of Hematology and Oncology Products
Mantle Cell Lymphoma (MCL)

• 5% of Non-Hodgkin Lymphoma
  – Approximately 3,000 cases per year in the US
• Clinically aggressive course
  – Median overall survival is ~ 3-5 years
  – Median survival after relapse declines to 1-2 years
• Available Treatment for Relapsed Disease: salvage chemotherapy, targeted therapies (no accepted standard of care)

<table>
<thead>
<tr>
<th>Approved Therapies (R/R MCL)</th>
<th>Bortezomib N=155</th>
<th>Lenalidomide N=134</th>
<th>Ibrutinib* (Accelerated approval) N=111</th>
</tr>
</thead>
<tbody>
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<td>26%(18, 34)</td>
<td>66%(56,75)</td>
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<td>CR, %</td>
<td>8%</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>Duration of response, median months</td>
<td>9.3(5.4, 13.8)</td>
<td>16.6(7.7, 26.7)</td>
<td>17.5(15.8, NR)</td>
</tr>
</tbody>
</table>

*Ibrutinib received BT Designation for R/R MCL in 2013

Reference ID: 4128797
Acalabrutinib

- Second generation, orally available, Bruton Tyrosine Kinase (BTK) inhibitor
  - more selective than 1st generation inhibitors
  - Different active site than first generation inhibitor
  - Potential less off-target toxicity

- Preliminary Clinical Evidence: ACE-LY-004
  - Trial Design: Phase 2, single-arm, open-label, multi-center study
  - Population: enrolled 124 patients with Mantle Cell Lymphoma that have relapsed after or were refractory to between 1 and 5 prior therapies
  - Dose: acalabrutinib 100mg po BID until disease progression or toxicity
  - Primary Endpoint: (ORR) defined as CR or PR per Lugano criteria as assessed by investigator
  - Key Secondary Endpoints: ORR per IRC, DOR
# ACE-LY-004: Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCL (N = 124) n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>99 (80)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median(Min, Max)</td>
<td>68 (42,90)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>71 (57.3)</td>
</tr>
<tr>
<td>1</td>
<td>44 (35.5)</td>
</tr>
<tr>
<td>2</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><strong>MIPI (Mantle Cell Lymphoma International Prognostic Index) Score</strong></td>
<td></td>
</tr>
<tr>
<td>Low Risk (0-3)</td>
<td>48 (38.7)</td>
</tr>
<tr>
<td>Intermediate Risk (4-5)</td>
<td>54 (43.5)</td>
</tr>
<tr>
<td>High Risk (6-11)</td>
<td>21 (16.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><strong>Median(range) number of prior therapies</strong></td>
<td>2 (1,5)</td>
</tr>
<tr>
<td><strong>Refractory Disease at Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (24.2)</td>
</tr>
<tr>
<td><strong>Number of Subjects with Extranodal Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>90 (72.6)</td>
</tr>
<tr>
<td>GI</td>
<td>63 (50.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>13 (10.5)</td>
</tr>
<tr>
<td></td>
<td>12 (9.7)</td>
</tr>
</tbody>
</table>
## ACE-LY-004 Efficacy Results

### Overall Response and Duration of Response by Investigator per Lugano 2014

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Acalabrutinib (N = 124)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>100 (80.6)</td>
<td>(72, 87)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>49 (39.5)</td>
<td>(31, 49)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>51 (41.1)</td>
<td>(32, 50)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (8.9)</td>
<td>(3.13)</td>
</tr>
<tr>
<td></td>
<td>10 (8.1)</td>
<td>(5.15)</td>
</tr>
<tr>
<td><strong>Duration of Response (DOR) (months), median (95% CI)</strong></td>
<td>NR (13.5, NR)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up (months), median (range)</strong></td>
<td>15.2 (0.3, 23.7)</td>
<td></td>
</tr>
</tbody>
</table>

### Duration of Response - All Treated Subjects Who Achieved PR or CR (ACE-LY-004)
Safety ACE-LY-004

<table>
<thead>
<tr>
<th>Duration of exposure (months)</th>
<th>(N = 124) [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>13.8 (0.1 to 22.1)</td>
</tr>
<tr>
<td>Min, Max</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinued Study Drug, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>54 (43.5)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>39 (31.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with any TEAEs, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 TEAE</td>
<td>61 (49.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with any SAE, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48 (38.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE leading to dose reduction, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

- Most Common TEAEs were Headache (38%), Diarrhea (31%), Fatigue (27%), Myalgia (21%)
- Most Common ≥ grade 3 TEAEs were Neutropenia (10.5%), Anemia (8.9%), Pneumonia (4.8%), Thrombocytopenia (4%), Diarrhea (3.2%)
- Deaths on study 27 (21%) : Disease progression - 22 (18%), AE – 1 (0.8%)
- Serious Adverse Events of Special Interest
  - Cardiac events- 8%(no reported events of atrial fibrillation)
  - Major hemorrhage- 0.8%
### Response Rates

<table>
<thead>
<tr>
<th>MCL</th>
<th>Acalabrutinib (N = 124)</th>
<th>Ibrutinib* (N = 111)</th>
<th>Bortezomib (N = 155)</th>
<th>Lenalidomide (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate (ORR) %, 95% CI</strong></td>
<td>80.6 (72.6, 87.2)</td>
<td>66 (56.2,74.5)</td>
<td>31 (24,39)</td>
<td>26 (18,34)</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>40</td>
<td>17</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>41</td>
<td>49</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td><strong>Duration of response (months)</strong></td>
<td>NR (13.5, NR)</td>
<td>17.5 (15.8, NR)</td>
<td>9.3 (5.4, 13.8)</td>
<td>16.6 (7.7, 26.7)</td>
</tr>
</tbody>
</table>

*accelerated approval

## Development Plan for Acalabrutinib

- NDA for acalabrutinib for proposed indication MCL received 6/13/2017 based on Study ACE-LY-004
  - Accelerated approval, expedited review ongoing
- Confirmatory Study Ongoing: Phase 3 trial(ACE-LY-308)
  - Bendamustine + Rituxan(BR) vs. BR + acalabrutinib(N=546)
  - Primary endpoint: PFS
- Sponsor has several ongoing studies in other hematologic malignancies(LLL, NHL)

Reference ID: 4128797
Summary

**DHP Recommendation:** Grant Breakthrough Therapy Designation

- Relapsed/Refractory Mantle Cell Lymphoma is a serious and life threatening condition
- Preliminary clinical evidence demonstrates substantial improvement over existing therapies on one or more clinically significant endpoints:
  - ORR of 80% (95% CI: 72, 87) (~2 fold higher ORR compared to available therapy)
  - CR of 40% (~2 fold higher CR rate compared to available therapy)

Reference ID: 4128797
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/s/

KAYLA J GARVIN
07/24/2017

ANN T FARRELL
07/24/2017
Good Morning Dr. Qazen,

I will need confirmation of any additions or changes to your team that will be in attendance to Friday’s AOM meeting at the Agency. Also I will need also need to know whether or not anyone from your team in attendance, holds green card (foreign visitor form will be required).

Please respond by today, 4 pm Monday July 24, 2017.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Good Morning Dr. Qazen,

Please confirm whether or not anyone from your team attending holds a green card. If so, they too will need to complete the foreign visitor form.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Dear Ashley,

Please find attached the final presentation slide deck for the Application Orientation Meeting with the FDA reviewers on July 28, 2017. I have also attached the Foreign Visitor Forms for my colleagues, David Holt and Michael Golden.

As discussed by phone last week, we will bring with us an electronic copy of the slides as well as any other backup slides necessary to support addressing questions that come up during the meeting.

Please let me know if you have any questions and if you could kindly confirm receipt of this email, that would be appreciated.

Thank you. I look forward to meeting you on the 28th.

Best Regards,
Yasameen Qazen

Yasameen Qazen, PharmD
Director Regulatory Science
Acerta Pharma, LLC
A Member of the AstraZeneca Group
2200 Bridge Parkway Ste 101
Redwood City, CA 94065
(o) 650-695-0086
(m) [锤] (b) (6)

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/s/

ASHLEY S LUCCI VAUGHN
07/24/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Please respond to the information request, below, via email by 12 pm am (ET) on Wednesday, July 26, 2017, and followed with a formal submission to the IND.

Clinical Pharmacology Information Request:

1. Your PBPK model under-predicted the plasma exposure of acalabrutinib and the active metabolite ACP-5862 (M27) following a single dose of 400 mg acalabrutinib (Table 7, report D8220C0003). Please provide rationale for this discrepancy and discuss the ability of your PBPK to predict exposure increases under drug-drug interaction scenarios, given the under-prediction at 400 mg acalabrutinib.

2. Clarify if ACP-5862 is the sole active metabolite of acalabrutinib. If not, provide a list of active metabolites and their PK characterization and pharmacological and biological activity such as plasma abundance, fraction unbound, and IC50 value(s).

3. We note that your PBPK model predicted AUC Ratio < 1 for active metabolite ACP-5862 (M27) when acalabrutinib is administered with concomitant CY3A induction. Given that M27 is formed via CYP3A metabolism from acalabrutinib and also metabolized by CYP3A and that acalabrutinib is a time-dependent inhibitor of CYP3A, there are competing mechanisms regarding the formation and elimination of M27. Discuss the validity of your M27 prediction under DDI scenarios and your confidence in the results.

4. Based on in vitro assessment, acalabrutinib is a substrate of BCRP. Clarify your plan regarding the use of concomitant BCRP inhibitors and whether you intend to conduct a clinical DDI study to assess the DDI risk of acalabrutinib as a BCRP substrate.
Kind Regards,

Ashley Lucci Vaughn, MS  
Regulatory Health Project Manager  
Division of Hematology Products/Office of Hematology and Oncology Products  
10903 New Hampshire Avenue  
White Oak Bldg. 22 Rm. 2354  
Silver Spring, MD 20993  
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
07/21/2017
Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Please respond to the information request, below, via email by 4 pm am (ET) on Friday, July 21, 2017, and followed with a formal submission to the IND.

**Information Request:**

1. Please provide carton labels for the [ ] count bottle.

Kind Regards,

Ashley Lucci Vaughn, MS  
Regulatory Health Project Manager  
Division of Hematology Products/Office of Hematology and Oncology Products  
10903 New Hampshire Avenue  
White Oak Bldg. 22 Rm. 2354  
Silver Spring, MD 20993  
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
07/18/2017
Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) dated and received June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acalabrutinib Capsules, 100 mg.

We acknowledge receipt of your correspondence, dated and received June 16, 2017, requesting a review of your proposed proprietary name, Calquence.

If the application is filed, the user fee goal date will be September 14, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Ashley LucciVaughn, Regulatory Project Manager, in the Office of New Drugs at (301) 796-5718.

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/

MARY POTHEN
06/22/2017
Good Morning Dr. Qazen,

I am confirming that the response request date and time should be 4 pm(ET) on Thursday, June 22, 2017.

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718

Dear Dr. Qazen,

Please refer to your new NDA 210259, received June 13, 2017 which provides an application for acalabrutinib, 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Please respond to the information request, below, via email by 4 pm am (ET) on Thursday, June 22, 2017, and followed with a formal submission to the IND.

**DSI Information Request:**

1. Confirm if the following address is where the sponsor’s clinical trial data, monitoring reports/clinical trial oversight documents and/or Masterfile’s
are located:

Acerta Pharma
2200 Bridge Parkway, Suite 101
Redwood City, CA 9406

2. Confirm if the above is the current address of the applicant

Kind Regards,

Ashley Lucci Vaughn, MS
Regulatory Health Project Manager
Division of Hematology Products/Office of Hematology and Oncology Products
10903 New Hampshire Avenue
White Oak Bldg. 22 Rm. 2354
Silver Spring, MD 20993
Phone: 301-796-5718
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/s/

ASHLEY S LUCCI VAUGHN
06/21/2017
NDA 210259

Acerta Pharma B.V.
Attention: Yasameen Qazen, PharmD
Director, Regulatory Science
2200 Bridge Parkway, Suite 101
Redwood City, CA  94065

Dear Dr. Qazen:

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

Name of Drug Product:  acalabrutinib capsule, 100 mg

Date of Application:  June 13, 2017

Date of Receipt:  June 13, 2017

Our Reference Number:  NDA 210259

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 12, 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), NO REG. 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 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, contact me at (301) 796-5718.

Sincerely,

{See appended electronic signature page}

Ashley Lucci Vaughn, MS  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research
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/s/

ASHLEY S LUCCI VAUGHN
06/20/2017
Hi Bill,

As a follow-up to the discussion during the preNDA meeting today regarding the upcoming NDA submission, please respond to the following information request by 4 pm EDT Tuesday June 6, 2017, followed by official submission to the IND.

To facilitate the selection of the clinical sites for inspection, submit a dataset (1 site per row) with the following information from clinical trial ACE-LY-004. 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 Acalabrutinib
- 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 acknowledge receipt of this request.

Thanks,

Beatrice Kallungal  
Senior Regulatory Health Project Manager  
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov
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/s/

BEATRICE A KALLUNGAL
06/06/2017
IND 118717

MEETING PRELIMINARY COMMENTS

Acerta Pharma B.V.
Attention: William Donaldson, BVSc, PhD
Vice President, Regulatory Affairs
2200 Bridge Parkway, Suite 202
Redwood City, CA 94065

Dear Dr. Donaldson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850).

We also refer to your March 30, 2017 requesting a meeting to determine the adequacy of the Sponsor’s clinical dossier based on pivotal study ACE-LY-004 for the proposed New Drug Application (NDA) for accelerated approval in support of the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Beatrice Kallungal, MS
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
  Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 2, 2017, 9 AM to 10 AM EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 118717
Product Name: Acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850)
Indication: For the treatment of patients with mantle cell lymphoma (MCL), who have received at least one prior therapy

Sponsor Name: Acerta Pharma B.V.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 2, 2017, 9 AM to 10 AM EDT, at FDA White Oak, between Acerta Pharma and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Acalabrutinib is a covalent Bruton tyrosine kinase (Btk) inhibitor being developed in oncologic indications. Acalabrutinib monotherapy is currently being studied in a single arm, Phase 2 study (ACE-LY-004) in subjects with previously treated mantle cell lymphoma (MCL), which completed enrollment and is now closed to enrollment.
An End of Phase 2 (EOP2) meeting was held with the Division of Hematology Products on March 21, 2016 to discuss the Sponsor’s plans for the clinical development of acalabrutinib in mantle cell lymphoma, including the potential for ACE-LY-004 to serve as the pivotal study for an NDA supporting an indication of previously treated MCL patients for accelerated approval.

On February 1, 2017 the Sponsor received Written Responses for a Type C meeting request to obtain feedback on the content and format of an acalabrutinib New Drug Application (NDA) for accelerated approval in support of the treatment of patients with MCL who have received at least one prior therapy.

On March 1, 2017 a Type B pre-NDA CMC meeting was held where there was agreement on the plan and timing for the stability package to be filed with the MCL NDA submission.

Acalabrutinib received orphan drug designation for the treatment of MCL. The Sponsor plans to submit the NDA for acalabrutinib for the treatment of patients with MCL who have received at least one prior therapy in Q2 2017, with the proposed confirmatory Phase 3 study ACE-LY-308 expected to be initiated by the time of submission.

The purpose of this pre-NDA meeting is to determine the adequacy of the Sponsor’s clinical dossier based on pivotal study ACE-LY-004, entitled “An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma,” for the proposed NDA for accelerated approval in support of the treatment of patients with MCL who have received at least one prior therapy. Further, the Sponsor aims to gain agreement with the Division on the overall content and format, excluding information in Module 3, which was discussed at a Type B, pre-NDA CMC meeting held on March 1, 2017 of the NDA to support the proposed indication.

2.0 DISCUSSION

Clinical
Question 1: Does the Agency agree that the efficacy (as assessed by both IRC and investigator) and safety results of pivotal study ACE-LY-004, along with data from other supportive studies, will support the filing and review of the NDA for accelerated approval in support of the proposed indication?

FDA Response to Question 1:
Based on our current understanding of your topline efficacy and safety data, it appears that they could support an application for the treatment of patients with mantle cell lymphoma who have failed at least 1 prior therapy. The Agency will conduct our own independent analysis of the datasets to confirm the efficacy claims. A decision on filing and subsequent review of the NDA will be made during the filing review.

We note that the study population includes patients with extranodal disease. In the NDA submission, provide assessments of response for all disease compartments [e.g., bone marrow (bone marrow assessments), gastrointestinal(endoscopy), pulmonary]. In addition characterization of progressive events for all patients will be important in the review of the
application. Provide brief narratives of the progressive events for all patients who progress to include descriptions of new sites of disease progression.

The Division notes that the determination of the accelerated approval pathway is an option based on available therapy at the time of regulatory action of your application. We note that confirmatory studies may be required as part of the accelerated approval pathway and these are usually ongoing at the time of the NDA submission. Provide an update on the status of Study ACE-LY-308 and timeline for submission of your proposed NDA for acalabrutinib.

At the meeting, discuss the proposed timelines for NDA submission, including whether a rolling review would be requested.

Question 2: Does the Agency suggest the data set and model files for the two PBPK modeling (ie, original and updated) studies be submitted with the original NDA or provided to the clinical pharmacology reviewers separately?

FDA Response to Question 2:
Yes. The data set and model files for the two PBPK modeling studies should be submitted with the original NDA. It is the agency’s expectation that the NDA submission should be complete at the time of Original NDA submission. Please refer to the following guidelines regarding general expectations of submitting pharmacometric data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDE R/ucm180482.htm

Nonclinical
Question 3: Does the Agency agree with the proposal to submit results of the dose-range finding pre- and postnatal development toxicity study along with the proposed safety update (Question 5)?

FDA Response to Question 3:
The decision on a need to conduct a pre and postnatal development (PPND) toxicity study will be made after our review of the definitive embryofetal development toxicity (EFD) results submitted with the NDA, and if needed, the PPND study could be done post-approval.

Regulatory
Question 4: Does the Agency agree that the proposed NDA should be considered for priority review?

FDA Response to Question 4:
The decision as to whether to grant priority or standard review will be made during the filing review.
Question 5: Does the Agency agree with the Sponsor’s proposal for the 90-day safety update?

FDA Response to Question 5:
Yes, your proposal is acceptable.

Question 6: Does the Agency agree that the proposed contents of Modules 1, 2, 4, and 5 are acceptable for the filing and review of the NDA for accelerated approval in support of the proposed indication (see Appendix 5)?

FDA Response to Question 6:
Refer to response to Question 1 regarding filing and review of your proposed application.

We reiterate our recommendation provided on January 30, 2017, that you include the following in your NDA application:

1. Address the following clinical pharmacology questions in Summary of Clinical Pharmacology (Module 2.7.2):
   a. What are the exposure-response relationships (dose-response, exposure-response) for efficacy and for safety?
   b. What influence do intrinsic and extrinsic factors have on exposure, efficacy, or safety?
   c. What dose and administration modifications are recommended for these factors?

2. Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the exposure-response datasets. Provide the relevant descriptive statistics for each of these variables.

3. Provide a table listing of patients with renal or hepatic impairment who have received acalabrutinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T. Bili, platelet count, etc. for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

   It is not clear from the proposed NDA Table of Contents if these recommendations will be addressed.

Question 7: Does the Agency agree with the Applicant’s plan to provide financial disclosure for covered studies ACE-LY-004 and ACE-CL-001?

FDA Response to Question 7:
Yes
### 3.0 OTHER IMPORTANT MEETING INFORMATION

#### DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 11, 2017 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

#### PREA REQUIREMENTS

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

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 PLLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.
Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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Corresponding names and titles of onsite contact:

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<th>Site Name</th>
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</table>

**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.”

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<tr>
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<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>III</td>
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<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
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</table>

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

```
- [m5]
  - datasets
    - bimo
      - site-level
```

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

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

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
05/26/2017
IND 118717

Acerta Pharma B.V.
c/o LBR Regulatory & Clinical Consulting Services, Inc.
Attention: Gregory Kelso, PhD
US Agent for Acerta Pharma B.V.
1125 Boone Aire Road
Florence, KY 41042

Dear Dr. Kelso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850).

We also refer to the meeting between representatives of your firm and the FDA on March 21, 2016. The purpose of the meeting was to obtain regulatory guidance and answers to specific questions on your plans for development of acalabrutinib for the treatment of mantle cell lymphoma (MCL).

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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

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:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

<table>
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<tr>
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<td>White Oak Building 22, Conference Room: 1419</td>
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<td></td>
<td>Silver Spring, Maryland 20903</td>
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<td>IND 118717</td>
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<td>Product Name:</td>
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<td>Indication:</td>
<td>Patients with mantle cell lymphoma (MCL) who have received at least one prior therapy</td>
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<tr>
<td>Meeting Chair:</td>
<td>R. Angelo de Claro, MD</td>
</tr>
<tr>
<td>Meeting Recorder:</td>
<td>Beatrice Kallungal, BS</td>
</tr>
</tbody>
</table>

FDA ATTENDEES

**Office of Hematology and Oncology Products/Division of Hematology Products**
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer

**Office of Biostatistics/Division of Biometrics V**
Lei Nie, PhD, Team Leader
Yun Wang, PhD, Reviewer

**Office of Clinical Pharmacology/Division of Clinical Pharmacology V**
Stacy Shord, PharmD, Reviewer

SPONSOR ATTENDEES
Hesham A Abdullah, MD, MSc, RAC, Vice President, Global Regulatory Affairs, Oncology & Immuno-Oncology, GMD, AstraZeneca
William Bushnell, MSc, Senior Director & Biometrics Team Leader, GMD, AstraZeneca
Flavia Borellini, PhD, CEO, Acerta Pharma
William Donaldson, BVSc, PhD, VP Regulatory Affairs, Acerta Pharma
Jane Huang, MD, VP Clinical Science, Acerta Pharma
Sandeep Inamdar, MD, BS, Sr. Medical Director, Acerta Pharma
IND 118717
Page 2

Raquel Izumi, PhD, Executive VP Clinical Development, Acerta Pharma
Priti Patel, MD, Senior Medical Director, Clinical Operations, Acerta Pharma
Greg Slatter, PhD, VP DMPK, Clinical Pharmacology, Acerta Pharma

Xiaolin Wang, ScD, VP of Biometrics, Acerta Pharma

1.0 BACKGROUND

Acalabrutinib is a covalent Bruton tyrosine kinase (Btk) inhibitor being developed in oncologic
indications. Acalabrutinib monotherapy is currently being studied in a single-arm, Phase 2 study (ACE-LY-004) in subjects with previously treated mantle cell lymphoma
(MCL), which completed enrollment and is now closed to enrollment.

The purpose of the meeting is to reach agreement on the development program for acalabrutinib
in treatment of patients with MCL and discuss the acceptability of the proposed Phase 3 studies
ACE-LY-308 (previously untreated MCL) for registration in the respective indications. The Sponsor would like to also discuss the potential
acceptability of results from the Phase 2 study (ACE-LY-004) to support accelerated approval
with ACE-LY-308 serving as the confirmatory study for traditional approval.

FDA sent Preliminary Comments to Acerta on March 16, 2016.

2.0 DISCUSSION

Question 1: Does the Agency agree the study design for ACE-LY-106 is adequate to determine
the safety of the acalabrutinib dosage to be evaluated in combination with BR in study ACE-LY-
308?

FDA Response:
Your proposed Phase 1b study appears adequately designed to determine a dose to be used
in combination with bendamustine and rituximab (BR).

Meeting Discussion:
No Discussion

Question 2: Does the Agency agree with the overall study design of the randomized, double-blind study of acalabrutinib plus BR versus placebo plus BR in subjects with previously
untreated MCL (ACE-LY-308)?

FDA Response:
No, we have several issues with your trial design.

It is unclear from the protocol how you intend to address patients who proceed to
transplantation after achieving a response. Although your entry criterion excludes subjects
for whom the goal of therapy is tumor debulking prior to stem cell transplantation, we
anticipate that a population of patients enrolled in the trial may still proceed to
transplantation after achieving a response. Describe how this issue will be addressed in the protocol and statistical analysis plan.

Clarify if you intend to enroll subjects with the blastoid or pleomorphic variant of mantle cell lymphoma. Clarify the expected proportion of subjects with these variants in the overall population.

We recommend that you also include measurement of Minimal Residual Disease (MRD) as an exploratory endpoint in your proposed trial.

**Meeting Discussion:**
No Discussion

**Question 3:** Does the Agency agree that positive results from study ACE-LY-308 may support the proposed indication of “Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of patients with ___ mantle cell lymphoma?”

**FDA Response:**
It is too early to discuss a proposed indication for acalabrutinib based on the Study ACE-LY-308.

**Meeting Discussion:**
No Discussion

**Question 4:** Does the Agency agree with the proposed statistical methods for ACE-LY-308 including interim analysis plan and methods for analysis of endpoints?

**FDA Response:**
We disagree with your two planned interim analyses for progression free survival (PFS), because those analysis results may be unreliable and overestimate actual treatment effect. Please also refer to additional statistical comments.

**Meeting Discussion:**
Regarding trial ACE-LY-308, the Agency provided feedback regarding concerns with the interim analysis of PFS. The Sponsor may submit revisions to the protocol for Agency feedback.

**Question 5:** Does the Agency agree that previously treated MCL constitutes an unmet medical need in the context of determining eligibility for Accelerated Approval in accordance with FDA guidance on Expedited Programs for Serious Conditions?

**FDA Response:**
We agree that relapsed or refractory mantle cell lymphoma is a serious condition. Eligibility for an accelerated approval pathway involves meeting all the qualifying criteria to include demonstrating a meaningful advantage over available therapies. Consideration for an accelerated approval of acalabrutinib for your proposed indication in previously treated MCL will be based on available therapy at the time of regulatory action.
**Question 6:** Does the Agency agree that should study ACE-LY-004 demonstrate sufficient magnitude of benefit (in terms of overall response rate (ORR) and duration of response (DOR)) that the data may be considered for Accelerated Approval of acalabrutinib in the proposed indication?

**FDA Response:**
An important consideration will be the durability of response. We recommend a minimum follow-up of 12 months for all responders for trial ACE-LY-004.

The Agency notes that the therapeutic landscape for the treatment of mantle cell lymphoma is rapidly evolving. The determination if an accelerated approval pathway is an option will be based on available therapy at the time of regulatory action of your application.

**Meeting Discussion:**
The Sponsor proposes their target for NDA submission in Q4 2016, based on a June 2016 data cutoff date with an estimated 8-month median duration of follow-up. The Agency emphasized the importance of 12-month follow-up for safety and efficacy data in the proposed population in order to support a breakthrough designation request (BTDR) and an application submission. For efficacy data, the Agency clarified minimum of 12-months follow-up for responders, which would start from the onset of response.

The Agency also explained that, as per PDUFA V regulations, applications must be complete at the time of submission. Late submissions may be allowed, but late submissions are inappropriate for data that are critical for the evaluation of safety and efficacy.

The Sponsor clarified that patients who are refractory to ibrutinib were not enrolled in trial ACE-LY-004.

**Question 7:** Does the Agency agree that positive results from either study ACE-LY-308 or may provide confirmation of clinical benefit for full approval should ACE-LY-004 garner Accelerated Approval?

**FDA Response:**
No, we have several issues regarding the trial design for Study ACE-LY-308 (see comments to questions 2 and 4 as well as additional statistical comments).

Lastly, the decision for an accelerated approval pathway for acalabrutinib in a previously treated MCL lymphoma population will be based on available therapy at the time of regulatory action of the application. See response to question 5.
Meeting Discussion:

The Sponsor inquired regarding the possibility of analysis of a subset of patients in trial ACE-LY-004 for duration of response. The Agency can review a proposal that is submitted by the Sponsor.

Additional comments:

Clinical Pharmacology

Statistical:
For study ACE-LY-004:
• Time-to-event endpoints, such as PFS and overall survival (OS), are not interpretable in this single-arm trial.
• Results on duration of response, in addition to overall response rate, are important in evaluating treatment effect in single-arm study.

For study ACE-LY-308:
• Your proposed disease assessment schedules are not consistent. If a subject remains on treatment, disease will be assessed every 16 weeks after cycle of 12 in study ACE-LY-308. If a subject discontinues the treatment for reasons other than disease progression, disease status will be assessed every 12 weeks. We recommend you revise the disease assessment schedules to every 12 weeks no matter the subject is on or off treatment.
• We discourage interim analyses for PFS, especially interim analyses of PFS based on small proportion of patients/events, because those analysis results may be unreliable and overestimate actual treatment effect.

• In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analysis of the primary endpoints cannot result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee a study-wise 1-sided type I error rate of 0.025.

• All patients should be followed for PFS until a PFS event occurs (progression or death) or until the data cutoff. Missing data/assessments of progression should be kept at a minimum. A substantial amount of missing data could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS. Sensitivity analyses, using different censoring mechanisms, should be performed to assess the robustness of the result of the primary analysis of PFS.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at

Reference ID: 3908303
DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER’s growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.
Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

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

II. Request for Subject Level Data Listings by Site

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

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:
III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry “Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.
Attachment 1  
Technical Instructions: 
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
  [m5]
  ├── datasets
  │   └── bimo
  │       └── site-level
```

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.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  

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

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

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

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA’s guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
   • A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
   • Other significant changes
   • Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The handouts used for this meeting has been appended to the meeting minutes.
Introduction:
The purpose of the meeting is to reach agreement on the development program for acalabrutinib in treatment of patients with MCL and to discuss the acceptability of the proposed Phase 3 studies for registration in the respective indications. The Sponsor would like to also discuss the potential acceptability of results from the Phase 2 study (ACE-LY-004) to support accelerated approval with ACE-LY-308 serving as the confirmatory study for traditional approval.
2.0 DISCUSSION

**Question 1:** Does the Agency agree the study design for ACE-LY-106 is adequate to determine the safety of the acalabrutinib dosage to be evaluated in combination with BR in study ACE-LY-308?

**FDA Response:**
Your proposed Phase 1b study appears adequately designed to determine a dose to be used in combination with Bendamustine and Rituximab (BR).

**Sponsor Response:**
Thank you for your comments.

**Question 2:** Does the Agency agree with the overall study design of the randomized, double-blind study of acalabrutinib plus BR versus placebo plus BR in subjects with previously untreated MCL (ACE-LY-308)?

**FDA Response:**
No, we have several issues with your trial design.

It is unclear from the protocol how you intend to address patients who proceed to transplantation after achieving a response. Although your entry criterion excludes subjects for whom the goal of therapy is tumor debulking prior to stem cell transplantation, we anticipate that a population of patients enrolled in the trial may still proceed to transplantation after achieving a response.

Describe how this issue will be addressed in the protocol and statistical analysis plan.

Clarify if you intend to enroll subjects with the blastoid or pleomorphic variant of mantle cell lymphoma. Clarify the expected proportion of subjects with these variants in the overall population.

We recommend that you also include measurement of Minimal Residual Disease (MRD) as an exploratory endpoint in your proposed trial.

**Sponsor Response:**
Acerta appreciates the Agency’s feedback regarding the design of the trial.

The sponsor agrees to amend the protocol to limit enrollment to include patients who are ≥ 65 years of age, or between the ages of 60-65 if they are determined to be transplant ineligible based on the opinion of the investigator. This patient population is less likely to proceed to transplant and as a result will provide a more homogenous patient population without significant censoring. We also agree to add MRD as an exploratory endpoint in this amendment.

Currently the protocol allows enrollment of patients with a blastoid or pleomorphic variant of MCL. In the frontline setting, 87% are classical variant and the remainder are comprised predominantly of small cell, blastoid, and pleomorphic variants. We anticipate that approximately 10-15 percent of patients to be of the non-classical variants (Robak, NEJM 2015 and McKay, BJH 2012). We recognize that ibrutinib has not demonstrated efficacy in this variant (Dreyling et al., Lancet Onc., 2015) and will further consider exclusion of these variants.
**Question 3:** Does the Agency agree that positive results from study ACE-LY-308 may support the proposed indication of “Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of patients with previously untreated mantle cell lymphoma.”?

**FDA Response:**
It is too early to discuss a proposed indication for acalabrutinib based on the Study ACE-LY-308.

**Sponsor Response:**
Acerta acknowledges the Agency response.

**Question 4:** Does the Agency agree with the proposed statistical methods for ACE-LY-308 including interim analysis plan and methods for analysis of endpoints?

**FDA Response:**
We disagree with your two planned interim analyses for PFS, because those analysis results may be unreliable and overestimate actual treatment effect. Please also refer to additional statistical comments.

**Sponsor Response:**
Acerta acknowledges the Agency comment regarding interim analyses which may be unreliable and overestimate actual treatment effect.

According to the proposed study design, two interim analyses will be conducted to assess for efficacy (Arm 1 when compared with Arm 2) with respect to the primary efficacy endpoint, IRC assessed PFS. The first interim analysis will occur when approximately 128 PFS events (45% of the primary event goal) have been observed. The second interim analysis will occur when approximately 174 PFS events (61% of the primary event goal) have been observed.

Based on the Agency feedback, Acerta will modify the protocol to require a minimum of 12 months follow-up for all patients prior to any interim analysis.

**Question 5:** Does the Agency agree that previously treated MCL constitutes an unmet medical need in the context of determining eligibility for Accelerated Approval in accordance with FDA guidance on Expedited Programs for Serious Conditions?

**FDA Response:**
We agree that relapsed or refractory mantle cell lymphoma is a serious condition. Eligibility for an accelerated approval pathway involves meeting all the qualifying criteria to include demonstrating a meaningful advantage over available therapies. Consideration for an accelerated approval of acalabrutinib for your proposed indication in previously treated MCL will be based on acalabrutinib at the time of regulatory action.

**Sponsor Response:**
Acerta acknowledges the Agency response. Please also refer to Question 6.
**Question 6:** Does the Agency agree that should study ACE-LY-004 demonstrate sufficient magnitude of benefit (in terms of overall response rate (ORR) and duration of response (DOR)) that the data may be considered for Accelerated Approval of acalabrutinib in the proposed indication?

**FDA Response:**
An important consideration will be the durability of response. We recommend a minimum follow-up of 12 months for all responders for trial ACE-LY-004.

The Agency notes that the therapeutic landscape for the treatment of mantle cell lymphoma is rapidly evolving. The determination if an accelerated approval pathway is an option will be based on available therapy at the time of regulatory action of your application.

**Sponsor Response:**
Acerta recognizes that the therapeutic landscape for MCL is rapidly evolving and agrees with the importance of durability of response in this setting.

The activity of acalabrutinib in CLL was recently published (Byrd, NEJM 2016), demonstrating an ORR and a durability of response that is consistent with the known activity of Btk inhibitors in CLL. Ibrutinib has shown durable responses in MCL in addition to demonstrating clinical benefit in CLL. Therefore, it is expected that the activity of acalabrutinib in mantle cell lymphoma will also be consistent with the class activity of Btk inhibitors in this setting. Additionally, acalabrutinib has demonstrated an acceptable safety profile which may be important for durability of response in this patient population.

Based on the preliminary data set from the LY-004 study (as of January 15th, 2016) provided in the meeting materials, acalabrutinib has an ORR of 73.7% and a CR rate of 34.2% with a median follow-up of 3.7 months. The sponsor acknowledges that the estimated median duration of response is based on a small number of events with limited follow-up. However, ORR supported by the duration of response and CR rate is likely to predict clinical benefit and therefore may serve as surrogate endpoints of durable benefit in the context of accelerated approval. Importantly, PET negative CR rates have been correlated in aggressive lymphomas to a longer progression free survival (Barrington SF, et al. JCO 2014).

The sponsor proposes to submit an initial NDA based on data from the pre-specified analysis in the LY-004 protocol comprised of all patients (n=124), 6 months after completion of enrollment. This reflects a median follow-up of 8 months in the 124 patients. We also propose to supplement the initial submission with data from an analysis that will provide additional efficacy data for 124 patients with 9 cycles of follow-up and approximately 88 patients with at least 12 cycles of follow-up.

**Question 7:** Does the Agency agree that positive results from either study ACE-LY-308 or study ACE-LY-004 may provide confirmation of clinical benefit for full approval should ACE-LY-004 garner Accelerated Approval?

**FDA Response:**
No, we have several issues regarding the trial design for Study ACE-LY-308 (see comments to questions 2 and 4 as well as additional statistical comments).
Lastly, the decision for an accelerated approval pathway for acalabrutinib in a previously treated MCL lymphoma population will be based on available therapy at the time of regulatory action of the application. See response to question 5.

**Sponsor Response:**
Acerta acknowledges the Agency comments and plan to amend the design of protocol LY-308 accordingly as referenced in the discussion of Question 4.

**Additional comments:**

**Clinical Pharmacology comment:**

**Sponsor Response:**

**Statistical comment:**

**For study ACE-LY-004:**
- Time-to-event endpoints, such as PFS and overall survival (OS), are not interpretable in this single-arm trial.
- Results on duration of response, in additional to overall response rate, are important in evaluating treatment effect in single-arm study.

**Sponsor Response:**
Acerta acknowledges the Agency response.
Sponsor Response:
The sponsor acknowledges your comments. See also response under Question 7.

For study ACE-LY-308:
• Your proposed disease assessment schedules are not consistent. If a subject remains on
treatment, disease will be assessed every 16 weeks after cycle of 12 in study ACE-LY-308,
(b)(4). If a subject discontinues the treatment for reasons
other than disease progression, disease status will be assessed every 12 weeks. We
recommend you revise the disease assessment schedules to every 12 weeks no matter the
subject is on or off treatment.

Sponsor Response:
Acerta acknowledges the Agency comment.

• We discourage interim analyses for PFS, especially interim analyses of PFS based on small
proportion of patients/events, because those analysis results may be unreliable and
overestimate actual treatment effect.

Sponsor Response:
Acerta acknowledges the Agency comment. Please also refer to Sponsor Response to Question 4

• In the absence of a statistically significant result for the primary analysis of the primary
endpoint, results based on secondary endpoints, subgroups, or further analysis of the primary
endpoints cannot result in (either singly or in combination) an efficacy claim. In the event
that there is a statistically significant result for the primary analysis of the primary endpoint,
those secondary endpoints that are significant after proper adjustment for multiplicity may be
included in the label. Please include in a future submission, any secondary endpoints for
which claims may be included in the labeling and how adjustments will be made for
multiplicity to guarantee a study-wise 1-sided type I error rate of 0.025.

Sponsor Response:
Acerta acknowledges the Agency response and agrees to provide the information requested in a
future submission.

• All patients should be followed for PFS until a PFS event occurs (progression or death) or
until the data cutoff. Missing data/assessments of progression should be kept at a minimum.
A substantial amount of missing data could undermine confidence in the PFS results of the
trial and may prevent a labeling claim on PFS. Sensitivity analyses, using different censoring
mechanisms, should be performed to assess the robustness of the result of the primary
analysis of PFS.

Sponsor Response:
Acerta acknowledges the Agency comment.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
03/25/2016
MEETING MINUTES

Acerta Pharma B.V.
c/o LBR Regulatory & Clinical Consulting Services, Inc.
Attention: Gregory L. Kelso, PhD
US Agent for Acerta Pharma B.V.
7000 Houston Road, Suite 18
Florence, KY 41042

Dear Dr. Kelso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)
of the Federal Food, Drug, and Cosmetic Act for ACP-196 (SCH 2046835/Org 300196-0; SCH
900850).

We also refer to the teleconference between representatives of your firm and the FDA on
December 10, 2014. The purpose of the meeting was to reach concurrence on the design of the
proposed Phase 3 clinical study in patients with [REDACTED] to determine the safety and efficacy of ACP-196 for the proposed indication and
to support product registration.

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

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-
9304.

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:
Meeting Minutes

Reference ID: 3672206
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B  
Meeting Category: End of Phase 1  
Meeting Date and Time: December 10, 2014; 1:00 PM - 2:00 PM EST  
Meeting Location: Teleconference  
Application Number: IND 118717  
Product Name: ACP-196 (SCH 2046835/Org 300196-0; SCH 900850)  
Indication: For the treatment of cancer (60)  
Sponsor/Applicant Name: Acerta Pharma B.V.  
Meeting Chair: R. Angelo de Claro, MD  
Meeting Recorder: Beatrice Kallungal, BS

Division of Hematology Products  
R. Angelo de Claro, MD, Medical Officer, Clinical Team Leader  
Karen McGinn, MS, RN, Senior Clinical Analyst

Division of Hematology, Oncology, Toxicology  
Haw-Jyh Chiu, PhD, Team Leader (Acting)  
Christopher Sheth, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V  
Bahrur Habtemariam, PharmD, Reviewer

Office of Biostatistics/Division of Biometrics V  
Lei Nie, PhD, Team Leader

SPONSOR ATTENDEES  
William Donaldson, BVSc, PhD, VP Regulatory Affairs, Acerta Pharma B.V.  
Julie Friedman, MPH, BScN, Sr. Director Program Management, Acerta Pharma B.V.  
Greg Kelso, PhD, Regulatory Consultant, LBR Regulatory & Clinical Consulting Services, Inc.  
Jesse McGreivy, MD, Consulting Medical Director, Hematology Oncology, Acerta Pharma B.V.  
Roger Ulrich, PhD, Chief Scientific Officer, Acerta Pharma B.V.
1.0 BACKGROUND

ACP-196 is a small molecule Bruton's tyrosine kinase (Btk) inhibitor, being developed by Acerta Pharma B.V. in oncologic (b)(4) indications. The requested meeting will focus on ACP-196 as single-agent treatment for patients (b)(4). The purpose of this meeting is to obtain regulatory guidance and answers to specific questions regarding the Sponsor’s plans for development of ACP-196 (b)(4) as outlined in their proposed Phase 3 protocol. The Sponsor would like to reach concurrence on

- the nonclinical toxicology program with regard to support of the proposed Phase 3 protocol and product registration;
- the clinical pharmacology program with regard to support of the proposed Phase 3 protocol and product registration;
- the design of the proposed Phase 3 clinical study in patients (b)(4) to a) confirm the safety and efficacy of ACP-196 for the proposed indication; and b) to support product registration.

FDA sent the End of Phase 1 Meeting Preliminary Comments to Acerta Pharma on December 5, 2014.

2. DISCUSSION

Preamble:

NONCLINICAL

Question 1: Does the Agency agree that the completed and planned nonclinical safety pharmacology and toxicology studies are adequate to support (b)(4) and product registration?
FDA Response:
Yes. However, the adequacy of the nonclinical studies will be determined during the New Drug Application (NDA) review.

Meeting discussion:
No discussion occurred.

CLINICAL PHARMACOLOGY

Question 2: Does the Agency agree that the completed and proposed clinical pharmacology studies are adequate to support (b)(4) and product registration?

FDA Response:
Yes, the proposed clinical pharmacology studies are acceptable. However, we have the following comments.

Meeting discussion:
No discussion occurred.

PEDIATRIC STUDIES

Question 3: Does the Agency agree that the Sponsor is exempt from conducting pediatric studies?

FDA Response:
No. However, if you receive Orphan designation for your proposed indication (b)(4), then you are not required to conduct pediatric studies.

Meeting discussion:
No discussion occurred.

CLINICAL

Question 4: Does the Agency agree the proposed method for confirmation of progression-free survival (PFS) and overall response rate (ORR) in study (b)(4) is acceptable?
FDA Response:
The proposed method is acceptable. However, refer to preamble regarding concerns with
the control arm.

Meeting discussion:
No discussion occurred.

Question 5: Does the Agency concur with the Sponsor’s proposal to use an Independent Review
Committee (IRC) to establish the efficacy of ACP-196 for the proposed indication, including the
proposed methodology and charter for the IRC’s review of efficacy data?

FDA Response:
Your proposal to use an IRC to assess efficacy is acceptable. However, refer to preamble
regarding concerns with the control arm.

The details of IRC charters are the Sponsor’s responsibility.

Meeting discussion:
No discussion occurred.

Question 6: Does the Agency concur with the Sponsor’s proposal to use a Data Monitoring
Committee (DMC) to ensure drug product safety as outlined in the DMC charter and to evaluate
efficacy in the planned interim analysis?

FDA Response:
We agree with your proposal to use a DMC to evaluate safety. However, refer to preamble
regarding concerns with the control arm.

We do not agree with your proposal to submit based on the planned interim analysis.
Refer also to response to Q8.

Meeting discussion:
No discussion occurred.

STATISTICAL METHODOLOGY

Question 7: Does the Agency concur with the sponsor’s proposed study size of 240 subjects, 2:1
allocation ratio (160 ACP-196 vs 80[4]) to be used for randomization and power
calculations for establishing efficacy?

FDA Response: No, refer to the preamble.

Meeting discussion:
No discussion occurred.
Question 8: Does the Agency concur with the Sponsor’s proposed plan for conducting a planned interim analysis?

FDA Response:
No. It is well recognized that the interim analysis results overestimate treatment effect size. The magnitude of estimated effect size in PFS is important in evaluating the benefit over the observed risk of the treatment as PFS does not measure direct clinical benefit. Therefore, we discourage claiming efficacy based on interim analysis of PFS. In addition, interim efficacy analysis of PFS would not provide adequate information for risk-benefit assessment.

Meeting discussion:
No discussion occurred.

Question 9: Does the Agency concur with the sponsor’s proposed hierarchical plan for evaluating the proposed primary and secondary endpoints?

FDA Response:
The primary endpoint of PFS assessed by IRC, and key secondary endpoint ORR assessed by IRC are acceptable. However, Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue and hematological improvement are not acceptable. See preamble regarding concerns with the control arm.

Meeting discussion:
No discussion occurred.

Question 10: Does the Agency agree that the proposed Statistical Analysis Plan will support product labelling claims regarding the primary and secondary outcome measures?

FDA Response:
No. See response to question 9.

Meeting discussion:
No discussion occurred.

OVERALL DEVELOPMENT PLAN AND PRODUCT REGISTRATION

Question 11: Does the Agency agree that the proposed development program, including data from the proposed Phase 3 study of ACP-196 vs supported by data from Phase 1 and Phase 2 studies, would be adequate for registration in the proposed indication?

FDA Response:
No. Refer also to preamble and response to question 2.
Meeting discussion:
No discussion occurred.

Additional comments:

Meeting discussion:
No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.
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/s/

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ROMEO A DE CLARO
12/12/2014
IND 118717

MEETING PRELIMINARY COMMENTS

Acerta Pharma
Attention: Gregory L. Kelso, Ph.D.
LBR Regulatory & Clinical Consulting Services, Inc.
7000 Houston Road, Suite 18
Florence, KY 41042

Dear Dr. Kelso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACP-196 (SCH 2046835/Org 300196-0; SCH 900850).

We also refer to your October 07, 2014 correspondence requesting a meeting to reach concurrence on the design of the proposed Phase 3 clinical study in patients to confirm the safety and efficacy of ACP-196 for the proposed indication and to support product registration.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Beatrice Kallungal, BS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

Preliminary Meeting Comments
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 1

Meeting Date and Time: December 10, 2014; 1:00 PM – 2:00 PM EST
Meeting Location: FDA White Oak Building 22, Conference Room: 1415

Application Number: IND 118717
Product Name: ACP-196 (SCH 2046835/Org 300196-0; SCH 900850)
Indication: For the treatment of (b)(4) (b)(4)
Sponsor/Applicant Name: Acerta Pharma BV

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 10, 2014 from 1:00 PM – 2:00 PM EST at FDA White Oak between Acerta Pharma and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

ACP-196 is a small molecule Bruton tyrosine kinase (Btk) inhibitor, being developed by Acerta Pharma BV in oncologic (b)(4) indications. The requested meeting will focus on ACP-196 as single-agent treatment for patients with (b)(4). The purpose of this meeting is to obtain regulatory guidance and answers to specific questions regarding the sponsor’s plans for development of ACP-196 (b)(4) as outlined in their proposed Phase 3 protocol. The Sponsor would like to reach concurrence on
the nonclinical toxicology program with regard to support of the proposed Phase 3 protocol and product registration;
the clinical pharmacology program with regard to support of the proposed Phase 3 protocol and product registration;
the design of the proposed Phase 3 clinical study in patients to a) confirm the safety and efficacy of ACP-196 for the proposed indication; and b) to support product registration.

2.0 DISCUSSION

Preamble:

NONCLINICAL

Question 1: Does the Agency agree that the completed and planned nonclinical safety pharmacology and toxicology studies are adequate to support and product registration?

FDA Response: Yes. However, the adequacy of the nonclinical studies will be determined during the NDA review.

CLINICAL PHARMACOLOGY

Question 2: Does the Agency agree that the completed and proposed clinical pharmacology studies are adequate to support and product registration?

FDA Response: Yes, the proposed clinical pharmacology studies are acceptable. However, we have the following comments.
PEDIATRIC STUDIES

Question 3: Does the Agency agree that the sponsor is exempt from conducting pediatric studies?

FDA Response:
No. However, if you receive Orphan designation for your proposed indication, then you are not required to conduct pediatric studies.

CLINICAL

Question 4: Does the Agency agree the proposed method for confirmation of PFS and ORR in study is acceptable?

FDA Response:
The proposed method is acceptable. However, refer to preamble regarding concerns with the control arm.

Question 5: Does the Agency concur with the sponsor’s proposal to use an IRC to establish the efficacy of ACP-196 for the proposed indication, including the proposed methodology and charter for the IRC’s review of efficacy data?

FDA Response:
Your proposal to use an IRC to assess efficacy is acceptable. However, refer to preamble regarding concerns with the control arm.

The details of IRC charters are the Sponsor’s responsibility.

Question 6: Does the Agency concur with the sponsor’s proposal to use a DMC to ensure drug product safety as outlined in the DMC charter and to evaluate efficacy in the planned interim analysis?

FDA Response:
We agree with your proposal to use a DMC to evaluate safety. However, refer to preamble regarding concerns with the control arm.

We do not agree with your proposal to submit based on the planned interim analysis. Refer also to response to Q8.
STATISTICAL METHODOLOGY

Question 7: Does the Agency concur with the sponsor’s proposed study size of 240 subjects, 2:1 allocation ratio (160 ACP-196 vs [redacted]) to be used for randomization and power calculations for establishing efficacy?

FDA Response: No, refer to the preamble.

Question 8: Does the Agency concur with the sponsor’s proposed plan for conducting a planned interim analysis?

FDA Response:
No. It is well recognized that the interim analysis results overestimate treatment effect size. The magnitude of estimated effect size in PFS is important in evaluating the benefit over the observed risk of the treatment as PFS does not measure direct clinical benefit. Therefore, we discourage claiming efficacy based on interim analysis of PFS. In addition, interim efficacy analysis of PFS would not provide adequate information for risk-benefit assessment.

Question 9: Does the Agency concur with the sponsor’s proposed hierarchical plan for evaluating the proposed primary and secondary endpoints?

FDA Response:
The primary endpoint of PFS assessed by IRC, and key secondary endpoint ORR assessed by IRC are acceptable. However, FACIT-fatigue and hematological improvement are not acceptable. See preamble regarding concerns with the control arm.

Question 10: Does the Agency agree that the proposed Statistical Analysis Plan will support product labelling claims regarding the primary and secondary outcome measures?

FDA Response:
No. See response to question 9.

OVERALL DEVELOPMENT PLAN AND PRODUCT REGISTRATION

Question 11: Does the Agency agree that the proposed development program, including data from the proposed Phase 3 study of ACP-196 vs [redacted], supported by data from Phase 1 and Phase 2 studies, would be adequate for registration in the proposed indication?

FDA Response:
No. Refer also to preamble and response to question 2.
3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product
registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS
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ABUSE POTENTIAL ASSESSMENT
Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.
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/s/

BEATRICE A KALLUNGAL
12/05/2014

Reference ID: 3668821
LATE-CYCLE COMMUNICATION DOCUMENTS
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210259

LATE-CYCLE MEETING MINUTES

Acerta Pharma B.V.
Attention: Yasameen Qazen, PharmD
Director, Regulatory Science
2200 Bridge Parkway, Suite 101
Redwood City, CA 94065

Dear Dr. Qazen:

Please refer to your New Drug Application (NDA) dated June 13, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for acalabrutinib capsule, 100 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 29, 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 Ashley Lucci Vaughn, Regulatory Project Manager at (301) 796-5718.

Sincerely,

{Tanya Wroblewski, MD}
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

Reference ID: 4164546
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Friday, September 29, 2017, 9:00 AM -10:00 AM EDT
Meeting Location: Teleconference

Application Number: NDA 210259
Product Name: Acalabrutinib
Applicant Name: Acerta Pharma B.V.

Meeting Chair: Tanya Wroblewski, MD, Acting Clinical Team Leader
Meeting Recorder: Ashley Lucci Vaughn, MS, Regulatory Project Manager

APPLICANT ATTENDEES
Jennifer Nicholson, MHA Senior Director, Regulatory Science
Davy Chiodin, PharmD, Vice President, Regulatory Science
Yasameen Qazen, PharmD Director, Regulatory Science Clinical Science
Priti Patel, MD Senior Medical Director, Clinical Development, Acerta Pharma
Naomi Hunder, MD, Vice President, Clinical Development, Acerta Pharma
Greg Slatter, PhD Vice President, DMPK, Clinical Pharmacology, Acerta Pharma
Cecile Krejsa, PhD Senior Director, Pharmacology and Toxicology, Acerta Pharma
Xiaolin Wang, ScD Vice President, Biometrics, Acerta Pharma
Xin Huang, PhD Director, Biostatistics, Acerta Pharma
Ed Tucker, BSc, MD, MRCP, MBA, SVP Medical Safety, Quality and Compliance
Nataliya Chernyukhin, MD Senior Director, Medical Safety Science, Acerta Pharma
Joseph Vu, MS, JD, Director, Regulatory CMC, Acerta Pharma
John Smart, PhD, Director, Regulatory CMC, AstraZeneca
Andrew Potts, BSc (Hons), Global Pharmaceutical Project Director, AstraZeneca
Maria Eriksson, PhD, PharmD, Global Supply and Strategy Director, AstraZeneca
Simon Hartas PhD, Sr Director, Global Product Development
Karen Capper BSc (Hons), Team Manager, Microbiology
Dave Laffan PhD, Director, Global Chemical Development

1.0 BACKGROUND
NDA 210259 was submitted on June 13, 2017 for acalabrutinib.

Proposed indication(s): For the treatment of patients with mantel cell lymphoma who have received at least one prior therapy

PDUFA goal date: February 13, 2017

FDA issued a Background Package in preparation for this meeting on September 27, 2017.
2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 5 minutes
   No substantive review issues have been identified at this time.

3. Discussion of Minor Review Issues – 5 minutes

4. Additional Applicant Data – 5 minutes (Applicant)

5. Information Requests – 5 minutes

CMC (sent September 21, 2017):

1) In response for question #7 dated August 25, 2017, you mentioned that Microbial limit testing method was validated using three lots of acalabrutinib capsules in accordance with USP<61> and <62>. Such report is not provided in the submission. Provide report supporting the claim.

2) We acknowledge you have submitted a Comparability Protocol that proposes alternative manufacturing sites at AstraZeneca, Sweden. [b](4) is also added as an additional stability testing site. You have stated in the Protocol that manufacturing procedures and testing procedures/specifications that will be approved in this NDA would be used at these sites. You also proposed that a CBE-30 be used for reporting on these additional manufacturing/testing facilities. The protocol states you will make three batches of drug product in the proposed facility but will provide only one batch of stability data for 3 months. This is not acceptable. You should provide stability data on all three batches in each packaging configuration [b](4).

6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

   - At this time, the Agency has identified three Postmarketing Requirements (PMRs) which were communicated to Acerta Pharma B.V. on September 25, 2017. A response was requested to the PMR document by September 29, 2017. As the review continues, the Agency is working towards final agreement with the applicant on all PMRs by October 16, 2017.

7. Major labeling issues – 5 minutes

   - The Agency sent revised labeling documents in tracked changes to Acerta Pharma B.V. on September 22, 2017 with requested response to labeling documents by September 29, 2017.

   - The Agency has a goal date of October 6, 2017, to send the Applicant the second round of labeling edits.

8. Review Plans – 5 minutes
• The user fee goal date for this submission is February 17, 2018. However, as we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review.

9. 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.

• Applicant inquired whether or not the Agency required the drug product batch number. The Agency does not require that you provide the batch number for the commercial drug product manufactured from drug substance batch C665/2.
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/s/

TANYA M WROBLEWSKI
10/06/2017
Acerta Pharma B.V.
Attention: Yasameen Qazen, PharmD
Director, Regulatory Science
2200 Bridge Parkway, Suite 101
Redwood City, CA  94065

Dear Dr. Qazen:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for Friday, September 29, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Ashley.luccivaughn@fda.hhs.gov, by Thursday, September 28, 2017.

If you have any questions, call Ashley Lucci Vaughn, Regulatory Project Manager, at (301) 796-5718.

Sincerely,

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

ENCLOSURE:
Late-Cycle Meeting Background Package
INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.
BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
   Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 5 minutes
   No substantive review issues have been identified at this time.
3. Discussion of Minor Review Issues – 5 minutes
4. Additional Applicant Data – 5 minutes (Applicant)
5. Information Requests – 5 minutes

CMC (sent September 21, 2017):

1) In response for question #7 dated August 25, 2017, you mentioned that Microbial limit testing method was validated using three lots of acalabrutinib capsules in accordance with USP<61> and <62>. Such report is not provided in the submission. Provide report supporting the claim.

2) We acknowledge you have submitted a Comparability Protocol that proposes alternative manufacturing sites at AstraZeneca, Sweden. is also added as an additional stability testing site. You have stated in the Protocol that manufacturing procedures and testing procedures/specifications that will be approved in this NDA would be used at these sites. You also proposed that a CBE-30 be used for reporting on
these additional manufacturing/testing facilities. The protocol states you will make three batches of drug product in the proposed facility but will provide only one batch of stability data for 3 months. This is not acceptable. You should provide stability data on all three batches in each packaging configuration.

6. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
   • At this time, the Agency has identified three Postmarketing Requirements (PMRs) which were communicated to Acerta Pharma B.V. on September 25, 2017. A response was requested to the PMR document by September 29, 2017. As the review continues, the Agency is working towards final agreement with the applicant on all PMRs by October 16, 2017.

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9. Wrap-up and Action Items – 5 minutes
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
09/27/2017