CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208772Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 208772           SUPPL # NA           HFD # 107

Trade Name  Alunbrig

Generic Name  Brigatinib

Applicant Name  ARIAD Pharmaceuticals Inc.

Approval Date, If Known  April 29, 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.

      NA

   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:

      NA
c) Did the applicant request exclusivity?  

YES ☒  NO ☐

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

Market exclusivity – 5 years  
Orphan Drug exclusivity – 7 years

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

YES ☐  NO ☒

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

NA

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.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐     NO ☐

If yes, explain:

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

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

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

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

Investigation #1

YES ☐     NO ☐

Investigation #2

YES ☐     NO ☐

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

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

Investigation #1

YES ☐     NO ☐
Investigation #2

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

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

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

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

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

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

   (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
Investigation #1

YES ☐  NO ☐

Explain:

Investigation #2

YES ☐  NO ☐

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: Leah Her
Title: Regulatory Health Project Manager
Date: April 24, 2017

Name of Division Director signing form: Martha Donoghue, M.D.
Title: Associate Director (Acting), Division of Oncology Products 2
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH S HER
04/24/2017

MARTHA B DONOGHUE
04/28/2017
PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA#: 208772
Supplement Number: _____  NDA Supplement Type (e.g. SE5): _____
Division Name: DOP2  PDUFA Goal Date: 4/29/17  Stamp Date: 8/29/16
Proprietary Name: Proposed as ALUNBRIG
Established/Generic Name: brigatinib
Dosage Form: tablets
Applicant/Sponsor: ARIAD Pharmaceuticals Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) NA
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Proposed as “ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.”

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____  Supplement #:_____  PMR #: _____
Does the division agree that this is a complete response to the PMR?
☐ Yes. Please proceed to Section D.
☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):
(a) NEW ☒ active ingredient(s) (includes new combination); ☑ indication(s); ☒ dosage form; ☒ dosing regimen; or ☐ route of administration?*
(b) ☐ No. PREA does not apply. Skip to signature block.

* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

Q3: Does this indication have orphan designation?
☒ Yes. PREA does not apply. Skip to signature block.
☐ No. Please proceed to the next question.
Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)
☐ No: Please check all that apply:
  ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

☐ Necessary studies would be impossible or highly impracticable because:
  ☐ Disease/condition does not exist in children
  ☐ Too few children with disease/condition to study
  ☐ Other (e.g., patients geographically dispersed): ______

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.
### Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in “gestational age” (in weeks).*

<table>
<thead>
<tr>
<th>Reason (see below for further detail):</th>
<th>minimum</th>
<th>maximum</th>
<th>Not feasible#</th>
<th>Not meaningful therapeutic benefit*</th>
<th>Ineffective or unsafe†</th>
<th>Formulation failed∆</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoneate</td>
<td>wk. ___</td>
<td>wk. ___</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>yr. ___ mo.</td>
<td>yr. ___ mo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? □ No; □ Yes.

Are the indicated age ranges (above) based on Tanner Stage? □ No; □ Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:
- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): ___

* Not meaningful therapeutic benefit:
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

∆ Formulation failed:
- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.**

Reference ID: 4033453
drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

<table>
<thead>
<tr>
<th>Deferrals (for each or all age groups):</th>
<th>Reason for Deferral</th>
<th>Applicant Certification †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>minimum</td>
<td>maximum</td>
</tr>
<tr>
<td>Neonate</td>
<td>_wk. _ mo.</td>
<td>_wk. _ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>_yr. _ mo.</td>
<td>_yr. _ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>_yr. _ mo.</td>
<td>_yr. _ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>_yr. _ mo.</td>
<td>_yr. _ mo.</td>
</tr>
<tr>
<td>All Pediatric Populations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
</tr>
</tbody>
</table>

Date studies are due (mm/dd/yy): ______

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: ______

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.
**Section D: Completed Studies (for some or all pediatric subpopulations).**

**Pediatric subpopulation(s) in which studies have been completed (check below):**

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>PeRC Pediatric Assessment form attached?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>Yes ☐ ☐ No ☐</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

**Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:**

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>__ wk. __ mo.</td>
<td>__ wk. __ mo.</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
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<tr>
<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
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<td>Other</td>
<td>__ yr. __ mo.</td>
<td>__ yr. __ mo.</td>
</tr>
<tr>
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<td>__ yr. __ mo.</td>
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<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

*IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cederpmhs@fda.hhs.gov) OR AT 301-796-0700.*

Reference ID: 4033453
Pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

<table>
<thead>
<tr>
<th>Population</th>
<th>minimum</th>
<th>maximum</th>
<th>Extrapolated from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adult Studies?</td>
</tr>
<tr>
<td>Neonate</td>
<td>__ wk. ___ mo.</td>
<td>__ wk. ___ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. ___ mo.</td>
<td>__ yr. ___ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. ___ mo.</td>
<td>__ yr. ___ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. ___ mo.</td>
<td>__ yr. ___ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>__ yr. ___ mo.</td>
<td>__ yr. ___ mo.</td>
<td>☐</td>
</tr>
<tr>
<td>All Pediatric Subpopulations</td>
<td>0 yr. 0 mo.</td>
<td>16 yr. 11 mo.</td>
<td>☐</td>
</tr>
</tbody>
</table>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH S HER
12/23/2016
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>208772</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 SES or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td>ALUNBRIG</td>
<td>Established/Proper Name:</td>
<td>brigatinib</td>
<td>Dosage Form:</td>
<td>tablets</td>
</tr>
<tr>
<td>RPM:</td>
<td>Leah Her</td>
<td>Applicant:</td>
<td>ARIAD Pharmaceuticals Inc.</td>
<td>Agent for Applicant (if applicable):</td>
<td></td>
</tr>
<tr>
<td>Division:</td>
<td>DOP2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

  - No changes
  - New patent/exclusivity (notify CDER OND IO)

  Date of check:

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

<table>
<thead>
<tr>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Proposed action</td>
</tr>
<tr>
<td>☑ User Fee Goal Date is 4/29/17</td>
</tr>
<tr>
<td>☑ Previous actions (specify type and date for each action taken)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Received</td>
</tr>
</tbody>
</table>

| Application Characteristics |

---

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: 4090897

Version: 2/12/16
Review priority: ☑ Standard  ☒ Priority
Chemical classification (new NDAs only):  ☑ Type I NME
(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)

<table>
<thead>
<tr>
<th>NDAs: Subpart H</th>
<th>BLAs: Subpart E</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ Accelerated approval (21 CFR 314.510)</td>
<td>☑ Accelerated approval (21 CFR 601.41)</td>
</tr>
<tr>
<td>☐ Restricted distribution (21 CFR 314.520)</td>
<td>☐ Restricted distribution (21 CFR 601.42)</td>
</tr>
<tr>
<td>☐ Approval based on animal studies</td>
<td>☑ Approval based on animal studies</td>
</tr>
</tbody>
</table>

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

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

Comments:

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

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    - Yes ☐  No notified 3/13/17
  - Indicate what types (if any) of information were issued
    - None
    - FDA Press Release
    - FDA Talk Paper
    - CDER Q&As
    - Other ASCO Burst

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    - No ☐  Yes ☒

- Patent Information (NDAs only)
  - Patent Information:
    - Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    - Verified
      - Not applicable because drug is an old antibiotic.

### CONTENTS OF ACTION PACKAGE

**Officer/Employee List**

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  - Included

- Documentation of consent/non-consent by officers/employees
  - Included
**Action Letters**

- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s) 4/28/17

**Labeling**

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included Final version received 4/27/17
  - Original applicant-proposed labeling
    - Included Received 8/29/16

- **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 Attached to Package Insert
  - Original applicant-proposed labeling
    - Included Received 8/29/16

- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most recent draft labeling
    - Included version dated January 27, 2017

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
    - 9/9/16 – Proprietary Name Granted
      - 9/6/16 Final Review / 9/6/16 TL Concurrency

- **Labeling reviews** *(indicate dates of reviews)*
  - RPM: None 11/7/16 / 11/8/16 TL Concurrency
  - DMEPA: None 2/15/17 Revised Review / 2/15/17 TL Concurrency
  - 1/6/17 Final Review / 1/6/17 TL Concurrency
  - DMPP/PLT (DRISEK):
    - None DMPP 2/9/17 Final Review / 2/9/17 TL, BC & OPDP Concurrency
  - OPDP: None 2/10/17 Pre-Decisional Review (PI)
  - 2/10/17 Pre-Decisional Review (Carton & Container)
  - SEALD: None
  - CSS: None
  - Product Quality: None
  - Other: None

**Administrative / Regulatory Documents**

Reference ID: 4090897
- **RPM Filing Review**/Memo of Filing Meeting *(indicate date of each review)*
  - All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee: 11/7/16 / 11/8/16 TL Concurrence
  - Not a (b)(2)

- **NDAs/NDA supplements only: Exclusivity Summary** *(signed by Division Director)*
  - Completed 4/28/17

- **Application Integrity Policy (AIP) Status and Related Documents**
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP: No
  - This application is on the AIP:
    - If yes, Center Director’s Exception for Review memo *(indicate date)*: No
    - If yes, OC clearance for approval *(indicate date of clearance communication)*: No
  - Pediatrics *(approvals only)*
    - Date reviewed by PeRC: 12/23/16 Pediatric Page
    - If PeRC review not necessary, explain: this product in this proposed indication was granted orphan drug designation on 4/28/16 (Designation # 15-5054)

- **Breakthrough Therapy Designation**
  - Breakthrough Therapy Designation Letter(s) *(granted, denied, an/or rescinded)*: N/A
  - 10/1/14

- **CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s)** *(include only the completed template(s) and not the meeting minutes)*
  - 9/23/14 Uploaded / 9/24/14 DD Concur

- **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)*
  - NA
  - *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*
  - 4/27/17 – Labeling IR (final comments)
  - 4/26/17 – Labeling IR (PI)
  - 4/26/17 – Labeling Tcon (uploaded 4/27/17)
  - 4/24/17 – Labeling IR
  - 4/19/17 – Labeling Tcon (uploaded 4/27/17)
  - 4/17/17 – Clinical IR
  - 4/3/17 – Labeling IR
  - 3/27/17 – Revised Clinical PMR IR
  - 3/27/17 – Clinical IR
  - 3/20/17 – Labeling IR (carton & container)
  - 3/13/17 – Clinical PMC
  - 3/10/17 – Clinical/OSI Tcon (uploaded on 3/27/17)
  - 3/8/17 – Clinical IR
  - 3/1/17 – Clinical IR (uploaded on 3/2/17)
  - 2/16/17 – Clinical IR
  - 2/13/17 – Clarification on LCM background (uploaded on 3/13/17)

---

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

**Reference ID:** 4090897
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>2/10/17</td>
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<tr>
<td>2/9/17</td>
<td>Clinical/OSI Tcon (uploaded on 2/27/17)</td>
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<td>2/7/17</td>
<td>Clinical IR</td>
</tr>
<tr>
<td>1/27/17</td>
<td>Labeling IR</td>
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<tr>
<td>1/17/17</td>
<td>CMC IR</td>
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<td>1/9/17</td>
<td>Labeling IR (carton &amp; container)</td>
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<tr>
<td>1/5/17</td>
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<td>CMC IR</td>
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<tr>
<td>12/22/16</td>
<td>Clinical PMR</td>
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<td>Clinical IR</td>
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<tr>
<td>12/20/16</td>
<td>Clin Pharm PMR/PMC</td>
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<tr>
<td>12/16/16</td>
<td>CMC IR</td>
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<td>Statistical IR</td>
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<td>Post Mid-Cycle Communication Agenda</td>
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<td>Clinical IR</td>
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<td>Acknowledge NDA</td>
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<tr>
<td>9/9/16</td>
<td>General Advice Letter (Application Orientation meeting)</td>
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<td>8/8/16</td>
<td>CMC IR</td>
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<tr>
<td>8/8/16</td>
<td>Acknowledge Presubmission</td>
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<tr>
<td>8/2/16</td>
<td>OSI IR</td>
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<tr>
<td>6/28/16</td>
<td>Acknowledge Presubmission</td>
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**Under IND 110935:**

5/25/16 – Grant Rolling Review

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/24/17</td>
<td>Wrap-Up Meeting Summary (uploaded 4/3/17)</td>
</tr>
<tr>
<td>2/28/17</td>
<td>SGE icon Dr. Szabo (uploaded 3/6/17)</td>
</tr>
<tr>
<td>2/28/17</td>
<td>SGE icon Dr. Arscott (uploaded 3/6/17)</td>
</tr>
<tr>
<td>2/6/17</td>
<td>Pre-LCM Summary (uploaded 4/3/17)</td>
</tr>
<tr>
<td>12/7/16</td>
<td>Dec 2016 Team Meeting Summary (uploaded 12/21/16)</td>
</tr>
<tr>
<td>11/29/16</td>
<td>Internal Mid-Cycle Summary (uploaded 1/3/17)</td>
</tr>
</tbody>
</table>

- **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)
| Minutes of Meetings                                      | 11/9/16 – Nov 2016 Team Meeting Summary (uploaded 12/21/16)  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If not the first review cycle, any end-of-review meeting (indicate date of mtg)</td>
<td>❌ N/A or no mtg</td>
</tr>
<tr>
<td>Pre-NDA/BLA meeting (indicate date of mtg)</td>
<td>✅ No mtg 4/15/16 (uploaded 4/19/16)</td>
</tr>
<tr>
<td>EOP2 meeting (indicate date of mtg)</td>
<td>❌ N/A 11/29/16 (uploaded on 1/3/17)</td>
</tr>
<tr>
<td>Mid-cycle Communication (indicate date of mtg)</td>
<td>❌ N/A 2/24/17 (uploaded on 3/15/17)</td>
</tr>
<tr>
<td>Late-cycle Meeting (indicate date of mtg)</td>
<td>3/2/16 pre-NDA / CMC only (uploaded on 3/8/16)</td>
</tr>
<tr>
<td>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)</td>
<td>6/30/15 Initial Multidisciplinary Meeting (uploaded 7/22/15)</td>
</tr>
</tbody>
</table>

| Advisory Committee Meeting(s)                          | ❌ No AC meeting                                           |

### Decisional and Summary Memos

| Office Director Decisional Memo (indicate date for each review) | None |
| Division Director Summary Review (indicate date for each review) | None 4/17/17 summary of final assessment and reference to Multidisciplinary Review for final review |
| Cross-Discipline Team Leader Review (indicate date for each review) | None 3/24/17 summary of final assessment and reference to Multidisciplinary Review for final review |
| PMR/PMC Development Templates (indicate total number) | None 4/27/17 amended Clin Pharm / 4/27/17 TL Concurrence / 4/27/17 DDS Concurrence |
|                                                         | 3/30/17 Clinical PMR / 3/30/17 TL Concurrence / 4/7/17 DDS Concurrence |
|                                                         | 3/21/17 Clinical PMC / 3/21/17 TL Concurrence / 3/21/17 DDS Concurrence |
|                                                         | 1/24/17 Clin Pharm 3 PMRs/2PMCs / 1/24/17 TL Concurrence / 1/24/17 DDS Concurrence |

### Clinical

<p>| Clinical Reviews                                      | ❌ No separate review 4/28/17 Final Review Concur – see Clinical/Statistics section of Multidisciplinary Review |
| Clinical Team Leader Review(s) (indicate date for each review) | 4/26/17 Final Assessment Concur – See Amended Memorandum |</p>
<table>
<thead>
<tr>
<th>Review Type</th>
<th>Date/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical review(s) <em>(indicate date for each review)</em></td>
<td>2/7/17 Final Assessment Concur – See Memorandum</td>
</tr>
<tr>
<td></td>
<td>9/30/16 Filing Review Concur – See Clinical Review</td>
</tr>
<tr>
<td></td>
<td>4/28/17 Final Review – see Clinical/Statistics section of Multidisciplinary Review</td>
</tr>
<tr>
<td></td>
<td>4/26/17 Amended Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review</td>
</tr>
<tr>
<td></td>
<td>2/7/17 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review</td>
</tr>
<tr>
<td></td>
<td>9/30/16 Filing Review</td>
</tr>
<tr>
<td>Social scientist review(s) *(if OTC drug) <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>Refer to Appendix 13.2 of the Multidisciplinary Review</td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <em>(indicate date of review/memo)</em></td>
<td></td>
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<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers <em>(indicate date of each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation <em>(indicate date of each review)</em></td>
<td>☒ N/A</td>
</tr>
<tr>
<td>- REMS Documents and REMS Supporting Document <em>(indicate date(s) of submission(s))</em></td>
<td>1/30/17 Final Review / 1/30/17 TL Concur</td>
</tr>
<tr>
<td>- REMS Memo(s) and letter(s) *(indicate date(s))</td>
<td></td>
</tr>
<tr>
<td>- Risk management review(s) and recommendations <em>(including those by OSE and CSS)</em> <em>(indicate date of each review and indicate location/date if incorporated into another review)</em></td>
<td></td>
</tr>
<tr>
<td>OSI Clinical Inspection Review Summary(ies) <em>(include copies of OSI letters to investigators)</em></td>
<td>☐ None requested 4/21/17 OSI Letter to Karen Reckamp, MD</td>
</tr>
<tr>
<td></td>
<td>4/21/17 OSI Letter to David Camidge, MD</td>
</tr>
<tr>
<td></td>
<td>OSI 4/21/17 Letter to Timothy Barrett, CEO</td>
</tr>
<tr>
<td></td>
<td>3/28/17 OSI Letter to Sang-We Kim, MD, PhD</td>
</tr>
</tbody>
</table>

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.)
<table>
<thead>
<tr>
<th>Clinical Microbiology</th>
<th>None</th>
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<tbody>
<tr>
<td>Clinical Microbiology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review</td>
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<td>Clinical Microbiology Review(s) <em>(indicate date for each review)</em></td>
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<table>
<thead>
<tr>
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<td>Statistical Division Director Review(s) <em>(indicate date for each review)</em></td>
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</tr>
<tr>
<td>Statistical Team Leader Review(s) <em>(indicate date for each review)</em></td>
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</tr>
<tr>
<td>Statistical Review(s) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
</tbody>
</table>

3/28/17 OSI Letter to Dong-Wan Kim, MD, PhD
2/9/17 Final Review / 2/10/17 TL Concurrency / 2/14/2017 BC Concur
4/28/17 Final Review Concur – see Statistical section of Multidisciplinary Review
2/10/17 Final Assessment Concur – See Memorandum
4/28/17 Final Review Concur – see Statistical section of Multidisciplinary Review
2/2/17 Final Assessment Concur – See Memorandum
10/3/16 Filing Review Concur – See Statistical Review
4/28/17 Final Review – see Statistical section of Multidisciplinary Review
2/2/17 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review
10/3/16 Filing Review
<table>
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<tr>
<td>✧ Clinical Pharmacology Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review  4/28/17 Final Review Concur – see Clinical Pharmacology section of Multidisciplinary Review  1/25/17 Final Assessment Concur – See Memorandum</td>
</tr>
<tr>
<td>Clinical Pharmacology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review  4/28/17 Final Review Concur – see Clinical Pharmacology section of Multidisciplinary Review  1/25/17 Final Assessment Concur – See Memorandum  10/26/16 Filing Review Concur – See Clinical Pharmacology Review</td>
</tr>
<tr>
<td>Clinical Pharmacology review(s) <em>(indicate date for each review)</em></td>
<td>☐ None  4/28/17 Final Review – see Clinical Pharmacology section of Multidisciplinary Review  1/25/17 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review  10/24/16 Filing Review  QT-IRT Review – 2/10/17 / 2/10/17 TL Concurrence  QT-IRT Review – 10/6/16 / 10/7/16 TL Concurrence</td>
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<tr>
<td>✧ OSI Clinical Pharmacology Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>☒ None requested</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>None</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Pharmacology/Toxicology Discipline Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>• ADP/T Review(s) (<em>indicate date for each review</em>)</td>
<td>No separate review 4/28/17 Final Review Concur – see Nonclinical section of Multidisciplinary Review</td>
</tr>
<tr>
<td>• Supervisory Review(s) (<em>indicate date for each review</em>)</td>
<td>No separate review 4/28/17 Final Review Concur – see Nonclinical section of Multidisciplinary Review 1/25/17 Final Assessment Concur – See Memorandum 9/27/16 Filing Review Concur – See Pharm/Tox Review</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews (<em>indicate date for each review</em>)</td>
<td>None 4/28/17 Final Review – see Nonclinical section of Multidisciplinary Review 1/23/17 Memorandum – summary of final assessment and reference to Multidisciplinary Review for final review 9/26/16 Filing Review</td>
</tr>
<tr>
<td><strong>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<em>indicate date for each review</em>)</strong></td>
<td>None</td>
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<tr>
<td><strong>Statistical review(s) of carcinogenicity studies (<em>indicate date for each review</em>)</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>ECAC/CAC report/memo of meeting</strong></td>
<td>None Included in P/T review, page</td>
</tr>
<tr>
<td><strong>OSI Nonclinical Inspection Review Summary (include copies of OSI letters)</strong></td>
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### Product Quality

<table>
<thead>
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<th>Product Quality Discipline Reviews</th>
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<tbody>
<tr>
<td>Tertiary review <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>Secondary review <em>(e.g., Branch Chief) (indicate date for each review)</em></td>
</tr>
</tbody>
</table>

- **Integrated Quality Assessment** *(contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*

- **Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)**
- **Environmental Assessment** *(check one) (original and supplemental applications)*
  - Categorical Exclusion *(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)*
  - Review & FONSI *(indicate date of review)*
  - Review & Environmental Impact Statement *(indicate date of each review)*

### Facilities Review/Inspection

- **Facilities inspections** *(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)*

---

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>
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<tbody>
<tr>
<td>✗ For all 505(b)(2) applications:</td>
<td>No changes</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>• Finalize 505(b)(2) assessment</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✗ For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>✗ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td></td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td>✔ Done 4/28/17</td>
</tr>
<tr>
<td>✗ Send a courtesy copy of approval letter and all attachments to applicant by fax or</td>
<td>✔ Done 4/28/17</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 4/28/17</td>
</tr>
<tr>
<td>confirming that applicant received courtesy copy of approval letter</td>
<td>(for ASCO burst</td>
</tr>
<tr>
<td>only)</td>
<td></td>
</tr>
<tr>
<td>✗ Ensure that proprietary name, if any, and established name are listed in the</td>
<td>✔ Done 4/28/17</td>
</tr>
<tr>
<td>Application Product Names section of DARRTS, and that the proprietary name is</td>
<td></td>
</tr>
<tr>
<td>identified as the “preferred” name</td>
<td></td>
</tr>
<tr>
<td>✗ Ensure Pediatric Record is accurate</td>
<td>✔ Done 4/28/17</td>
</tr>
<tr>
<td>✗ Send approval email within one business day to CDER-APPROVALS</td>
<td>✔ Done 4/28/17</td>
</tr>
</tbody>
</table>

Reference ID: 4090897
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/s/

LEAH S HER
04/28/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached FDA’s edits and comments to your revised package insert (PI) labeling submitted on April 26, 2017.

If you have no additional questions and agree to these edits, please send me via email a clean, word version of the final label, followed by a formal submission via the gateway as soon as possible, following the email.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
04/27/2017
Date: April 27, 2017
From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2
Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

Discussion of proposed package insert

Date and Time of Teleconference: April 19, 2017, approximately 2:30 – 3:00 PM (EST)

FDA Participants:
- Martha Donoghue, Associate Director (Acting), DOP2
- Naomi Horiba, Clinical Reviewer, DOP2

Sponsor Participants:
- Melody Brown, Vice President, Regulatory Affairs (Takeda)
- Daniel Bollag, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Quality
- Guilin Huang, Director, Regulatory Affairs
- Shreya Mehta, Senior Associate, Regulatory Affairs
- David Kerstein, Senior Medical Director, Clinical Research and Development
- Stephanie Lustgarten, Senior Director, Biostatistics and Statistical Programming
- William Reichmann, Senior Biostatistician, Biostatistics and Statistical Programming
- Benjamin Exter, Senior Director, Global Pharmacovigilance (Takeda)
- Dennis Vargo, Global Safety Lead, Global Pharmacovigilance (Takeda)

This was a FDA-initiated teleconference for pending New Drug Application (NDA) 208772 received on August 29, 2016, for the proposed use of brigatinib for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

The objective of this teleconference was to discuss the proposed package insert received on April 11, 2017.

Summary of the Tcon:

The following section of the label was discussed:
- Section 5.1 Interstitial Lung Disease(ILD)/Pneumonitis

FDA and ARIAD discussed the presentation of the information and values regarding pulmonary adverse reactions and pneumonitis. FDA stated FDA will propose edits for Section 5.1 for ARIAD’s consideration and suggested that in the interim, ARIAD should also consider different approaches for this section.
Additionally, FDA also requested ARIAD to re-order Table 3 Adverse Reactions in Section 6.1 to reflect a descending incidence of toxicities rather than place them in an alphabetical order.

Attachments:
- Post tcon ARIAD’s proposal regarding Section 5.1 and Table 3 of Section 6.1 sent via email on 4/20/17
ARIAD’s Proposal for Brigatinib USPI

During the 4/19/2017 t-con, FDA and ARIAD discussed Section 5.1 of brigatinib USPI and Table 3. Based on the Agency’s advice, ARIAD proposes the following approach to update Section 5.1 and Table 3.

ARIAD’s Proposal for Section 5.1

ARIAD proposes to retain the current title of Section 5.1. We suggested edits (see red text below) to second paragraph of this section. The changes proposed to the second paragraph captures the case definitions of pulmonary events agreed upon by the FDA. It also characterizes the nature of early onset pulmonary events reported as dyspnea and pneumonia but for which ILD/pneumonitis could not be ruled out.

5.1 Interstitial Lung Disease (ILD)/Pneumonitis and [b] [c]

Severe, life-threatening, and fatal pulmonary adverse reactions [b] [c] interstitial lung disease (ILD)/pneumonitis have occurred [b] [c] with ALUNBRIG.

[b] [c]

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of [b] [c]. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 [b] [c] either resume ALUNBRIG with dose reduction according to Table 1 [b] [c] after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 [b] [c] or recurrence of Grade 1 or 2 [b] [c] [see Dosage and Administration (2.2) and Adverse Reactions (6.1)].
ARIAD’s Proposal for Table 3 in the USPI

FDA advised to re-order the Table 3 by listing the SOC in a descending order that has the highest frequency for an ADR in Arm B (all grades). The ADR table below (Table 3 in the USPI) was prepared to replace Table 3 in our 4/10/2017 label.

Table 3: Adverse Reactions in ≥ 10% (All Grades*) or ≥ 2% (Grades 3-4) of Patients by Dose Group in (N=219)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>90 mg once daily group</th>
<th>90–180 mg once daily group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>Abdominal Pain¹</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders And Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue²</td>
<td>29</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic And Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea²</td>
<td>27</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>ILD/Pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache†</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>15</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>90 mg once daily group</td>
<td>90→180 mg once daily group</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td></td>
<td>Grades 3-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (b)</td>
<td>21 (b)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12 (b)</td>
<td>17 (b)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (b)</td>
<td>15 (b)</td>
</tr>
<tr>
<td>Myalgia†</td>
<td>0 (b)</td>
<td>15 (b)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (b)</td>
<td>14 (b)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11 (b)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal And Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism And Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>22 (b)</td>
<td>15 (b)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Disturbance**</td>
<td>(b)</td>
<td>10 (b)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>(b)</td>
<td>10 (b)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (b)</td>
<td>0 (b)</td>
</tr>
</tbody>
</table>

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
†Includes abdominal distension, abdominal pain, and epigastric discomfort
‡Includes asthenia, fatigue
§Includes dyspnea and exertional dyspnea
¶Includes headache and sinus headache
#Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash
††Includes musculoskeletal pain and myalgia
**Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment
†††Includes one Grade 5 event
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/s/

LEAH S HER
04/27/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 27, 2017
From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2
Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Discussion of proposed package insert

Date and Time of Teleconference: April 26, 2017, approximately 10:30 – 11:00 AM (EST)

FDA Participants:
Martha Donoghue
Steven Lemery
Naomi Horiba
Leah Her
Associate Director (Acting), DOP2
Clinical Team Leader, DOP2
Clinical Reviewer, DOP2
Regulatory Health Project Manager, DOP2

Sponsor Participants:
Melody Brown
Patricia Thomas
Daniel Bollag
Guilin Huang
Shreya Mehta
Sergio Santillana
David Kerstein
Ronald Knickerbocker
Stephanie Lustgarten
William Reichmann
Benjamin Exter
Dennis Vargo
Vice President, Regulatory Affairs (Takeda)
Senior Director, Regulatory Affairs (Takeda)
Senior Vice President, Regulatory Affairs, Pharmacovigilance and Quality
Director, Regulatory Affairs
Senior Associate, Regulatory Affairs
Vice President, Clinical Research and Development, Chief Medical Officer
Senior Medical Director, Clinical Research and Development
Vice President, Biomedical Data Sciences & Information
Senior Director, Biostatistics and Statistical Programming
Senior Biostatistician, Biostatistics and Statistical Programming
Senior Director, Global Pharmacovigilance (Takeda)
Global Safety Lead, Global Pharmacovigilance (Takeda)

This was a FDA-initiated teleconference for pending New Drug Application (NDA) 208772 received on August 29, 2016, for the proposed use of brigatinib for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

The objective of this teleconference was to discuss the proposed package insert received on April 25, 2017.

Prior to the teleconference on April 26, 2017, ARIAD submitted additional clarification items via email (attached to this tcon memo).

Reference ID: 4090567
Summary of the Tcon:

The following sections of the label were discussed:
- Section 2.1 Recommended Dosing
- Section 5.1 Interstitial Lung Disease (ILD)/Pneumonitis
- Section 5.3 Bradycardia
- Section 6.1 Clinical Trial Experience
- Section 14 Clinical Studies

FDA and ARIAD also briefly discussed the proposed changes for the statement pertaining to paresthesia or peripheral sensory neuropathy in Section 6.1. FDA requested that ARIAD provide an aggregate percentage that expresses the per patient incidence of either paresthesia or peripheral sensory neuropathy in the 90→180 mg group in order to avoid double counting of patients, given the similarity between patients with paresthesia or peripheral sensory neuropathy.

ARIAD also requested FDA’s advice on [Redacted] for consistency between Sections 5 and 6. FDA stated that ARIAD could use the values in Section 6. FDA also stated that in general [Redacted]

Attachments:
- Pre-tcon ARIAD’s clarification requests sent via email on 4/26/17
- Post-tcon FDA’s follow-up regarding peripheral neuropathy in Section 6.1 sent via email on 4/26/17

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

Reference ID: 4090567
Hi Guilin,

The clinical reviewer has the following comment regarding peripheral neuropathy.

**Comment:**

The per-patient composite incidence of peripheral neuropathy and paresthesia was 11.8% in Arm A and 12.7% (including one each Grade 3 peripheral neuropathy and paresthesia) in Arm B. Please include “peripheral neuropathy” under “Nervous System Disorders” in Table 3 of the label, and include a footnote to describe the preferred terms (peripheral neuropathy and paresthesia).

Please delete the following statement (b)(4) under Table 3

Kindly confirm receipt.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Room 2315
Silver Spring, MD 20903
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov
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/s/

LEAH S HER
04/27/2017
Hi Guilin,

The clinical reviewer has the following comment regarding peripheral neuropathy.

Comment:

The per-patient composite incidence of peripheral neuropathy and paresthesia was 11.8% in Arm A and 12.7% (including one each Grade 3 peripheral neuropathy and paresthesia) in Arm B. Please include “peripheral neuropathy” under “Nervous System Disorders” in Table 3 of the label, and include a footnote to describe the preferred terms (peripheral neuropathy and paresthesia).

Please delete the following statement (delete this sentence under Table 3)

Kindly confirm receipt.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Room 2315
Silver Spring, MD 20903
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov
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/s/

LEAH S HER
04/27/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached FDA’s edits and comments to your revised package insert (PI) labeling submitted on April 25, 2017. Please provide your response via email as soon as possible, and follow that with a formal submission to the NDA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From ARIAD” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From ARIAD” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
04/26/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached FDA’s edits and comments to your revised package insert (PI) labeling submitted on April 11, 2017. Please provide your response via email as soon as possible but no later than 10 AM (EST), Tuesday, April 25, 2017, and follow that with a formal submission to the NDA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From ARIAD” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From ARIAD” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
04/24/2017
Date: April 17, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Clinical Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response via email as soon as possible but no later than 12 PM (EST) on Tuesday, April 18, 2017, and follow that with a formal submission to the NDA.

Comment:

1. Please provide a line listing of individual IRC assessed intracranial responses for the ITT population.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
04/17/2017
Application: NDA 208772
Product: Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date: August 29, 2016
Received Date: August 29, 2016
Applicant: ARIAD Pharmaceuticals Inc.
Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees: Martha Donoghue, Naomi Horiba, Thomas Ly, Joyce Crich, Olen Stephens, Leah Her, Whitney Helms, Ruby Leong, Lauren Iacono-Connor, Elizabeth Everhart, Rowe Medina, Nazia Fatima, Connie Chen

* The Review Team was reminded that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

1. Review Status
   Discussion: Applicant’s NDA submission contents and requests previously discussed. No discussion occurred.

2. Upcoming Application Milestone
   Discussion: The Team briefly discussed the upcoming timelines.

3. Team Updates
   Discussion: The Team discussed ARIAD’s 3/1/17 responses to the IR pertaining to the changes to the IRC database and overall implications of this specific item for the labeling. The Team commented on the lack of clarity regarding the basis for the changes and discussed various methods to verify the information. An IR will be issued to obtain information regarding the source of change. The Team also discussed ARIAD’s 3/7/17 proposal pertaining to the clinical PMC intended to better characterize the duration of intracranial response. A teleconference will be scheduled to discuss obtaining access to the source documentation for the IRC changes, and to discuss and finalize the clinical PMC language.

4. Labeling
   Discussion: The Team discussed the addition of the hyperglycemia language to the label. DRISK will assess to determine if an addendum to the final DRISK review is needed. CMC stated that the carton and container labeling will need to be updated in terms of temperature to align with the definition and syntax of USP-defined controlled room temperature. An IR will be issued for this change. This change has already been included in the PI, which is still under review.

Reference ID: 4078928
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/s/

LEAH S HER
04/03/2017
Wrap-Up Meeting Summary
March 24, 2017

Application: NDA 208772
Product: Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date: August 29, 2016
Received Date: August 29, 2016
Applicant: ARIAD Pharmaceuticals Inc.

Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees: Martha Donoghue, Steven Lemery, Naomi Horiba, Monica Hughes, Leah Her, Thomas Ly, Hong Zhao, Ruby Leong, Whitney Helms, Anwar Goheer, Olen Stephens, Joyce Crich, Steven Kinsley, Janine Stewart, Elizabeth Everhart, Nazia Fatima, Rowe Medina, Lauren Iacono-Connor, Tri Bui Nguyen

1. Upcoming Application Milestones

Discussion: The schedule of this application was discussed. The review of the application is on track. The current targeted action date is April 28, 2017, as the PDUFA goal date is Saturday, April 29, 2017. The Team discussed that this date could change depending on the status of the remaining items in the application.

2. Discipline Specific Reviews of Application

Discussion: No discipline specific issues were discussed. This application is under the shared review pilot. All core disciplines (except CMC, a separate review uploaded in DARRTS) have completed their portions in the shared review and have uploaded a memorandum to this effect in DARRTS.

3. Consults Status

Discussion: The Team briefly discussed the status of the review of the source documentation for the IRC database changes at the imaging vendor, submitted to the NDA on 3/13/17. This review is expected to complete by end of the week of 3/27/17. A follow-up with ARIAD may be needed for access of the XML file.

All consults, including SGEs, have been completed. Refer to Discussion Item 4 below for additional discussion.

4. Labeling Discussion

Discussion: A decision on inclusion of the IRC-assessed data in the PI will be tabled until completion of the source documentation review for the IRC database changes. DRISK will review the hyperglycemia language addition to the PI to determine if an addendum to the DRISK review is needed. The update to the PPI to include the hyperglycemia language and to address additional internal comments is currently ongoing and is expected to be completed by mid-week of 3/27/17. The Team also discussed CPK evaluation and potential correlation to muscle pain. An IR will be sent to ARIAD to request an analysis be provided.

The Team briefly discussed ARIAD’s proposal regarding the order of the storage temperature in the carton and container labeling in response to FDA’s 3/20/17 IR, and stated that the proposed approach was acceptable. RPM will notify ARIAD and to request that the proposal is formally submitted to the NDA.

Reference ID: 4078929
In terms of labeling discussions with ARIAD, the Team stated that the label may be ready to be sent out to ARIAD by end of the week of 3/27/17 or early week of the 4/3/17.

5. PMCs/PMRs

Discussion: The Team briefly discussed a minor revision to the agreed upon clinical PMR. An IR will be sent to ARIAD for agreement of the revised language.

The single clinical PMC, and 3 clinical pharmacology PMRs and 2 PMCs have been agreed upon, and the PMR/PMC development templates have been completed.

The Team confirmed that no new PMRs/PMCs are anticipated.

6. Press Release and Burst

Discussion: The Team briefly discussed OMA’s inquiry regarding the need for a press release. RPM will follow up with the Office Director on whether a press release is necessary for this application. An ASCO Burst will be drafted.

7. Discussion of Proposed Action To be Taken

Discussion: The Team confirmed that the action will be accelerated approval.

8. Discussion of Sign-Off Procedure and Schedule

Discussion: The Team briefly reviewed the sign off procedure of the shared review for an anticipated action date of 4/28/17. The Team also discussed formatting and other pending issues pertaining to the shared review document.

9. Other Pending Items

Discussion: The Team briefly reviewed other pending items in the application.

10. MISC Items or Issues

Discussion: The Team confirmed that there were no other outstanding issues or discussion items at this point in time.
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/s/

LEAH S HER
04/03/2017
Date: April 3, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

Labeling Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached FDA’s edits and comments to your revised package insert (PI) labeling submitted on February 14, 2017. Please provide your response via email as soon as possible but no later than 4 PM (EST), Monday, April 10, 2017, and follow that with a formal submission to the NDA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From ARIAD” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From ARIAD” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 4079132
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/s/

LEAH S HER
04/03/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than 4 PM (EST) on Wednesday, March 29, 2017, and follow that with a formal submission to the NDA.

Comment:

1. Please perform an analysis correlating CPK elevation with any preferred term event of myalgia or muscle spasm.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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//s//

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LEAH S HER
03/27/2017
Date: March 27, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

Revised Proposed Post Marketing Requirement

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We also refer to our December 22, 2016, communication pertaining to a clinical Post Marketing Requirement (PMR) as required under 21 CFR 314.510, and your January 5, 2017, response formally submitted to the NDA, wherein you provided agreement to the PMR and your proposed scheduled milestone dates for our review. We further refer to our February 24, 2017, Late Cycle Meeting, wherein we stated that no additional discussion was needed for this PMR.

Upon review, we have determined that the PMR language will need to be revised to require a confirmation of clinical benefit as opposed to establishing superiority over existing therapies. Provide your agreement to the below proposal. Please provide a response as soon as possible but no later than 4 PM (EST), Friday, March 31, 2017.

POST MARKETING REQUIREMENT

Clinical

1. Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority that verifies and describes the clinical benefit of brigatinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

The timetable you proposed in your January 5, 2017, submission is below:

PMR/PMC Schedule
Milestones:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Completion</td>
<td>March 31, 2020</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>December 31, 2020</td>
</tr>
</tbody>
</table>

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 4075289
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/s/

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LEAH S HER
03/27/2017
Date: March 27, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Discussion of a clinical PMC and OSI findings – follow-up

Date and Time of Teleconference: March 10, 2017, approximately 12:30 – 1:00 PM (EST)

FDA Participants:
Martha Donoghue  Associate Director (Acting), DOP2
Steven Lemery    Clinical Team Leader, DOP2
Naomi Horiba     Clinical Reviewer, DOP2
Leah Her         Regulatory Health Project Manager, DOP2
Thomas Ly        Statistical Reviewer, DBV
Lauren Iacono-Connor OSI Reviewer, GCPAB
Susan Thompson   OSI Team Leader, GCPAB

Sponsor Participants:
Daniel Bollag     Senior Vice President, Regulatory Affairs, Pharmacovigilance, and Quality
David Kerstein   Senior Director, Clinical Research and Development
Guilin Huang      Director, Regulatory Affairs
Melody Brown      Vice President, Regulatory Affairs (Takeda)
Ronald Knickerbocker Vice President, Biomedical Data Sciences & Information
Sergio Santillana Vice President, Clinical Research and Development, Chief Medical Officer
Shreya Mehta      Senior Associate, Regulatory Affairs
Stephanie Lustgarten Senior Director, Biostatistics and Statistical Programming
Timothy Maines    Vice President, Quality
Tim Clackson      President of Research & Development, Chief Scientific Officer

This was a FDA-initiated teleconference for a follow-up discussion regarding a clinical Postmarketing Commitment (PMC) and regarding IRC database changes identified during the FDA inspection of [redacted]. On March 7, 2017, ARIAD provided via email, a proposal for the clinical PMC for intracranial responses. On March 9, 2017, ARIAD provided via email, a proposal to provide information to access the source documentation to verify the information regarding IRC database changes submitted formally to the NDA on March 1, 2017.

In advance of this meeting on March 8, 2017, FDA provided an agenda.
The correspondences described above are attached to this tcon memo.

IRC database changes
FDA acknowledged the receipt of ARIAD’s 3/9/17 proposal to provide the source documentation for the IRC database changes. FDA requested and received ARIAD’s confirmation that data being proposed to be provided are actual source records from the MINT lesion system. FDA stated the ARIAD’s proposal to provide the information appeared acceptable; however, FDA also requested the same information in a transport file format. ARIAD stated that they would follow up with the vendor, [redacted], to determine the feasibility of FDA’s request. In terms of timing, ARIAD committed to providing the requested information by early week of 3/13/17.

FDA also asked why the information provided by ARIAD was not readily available during FDA’s inspection of [redacted]. ARIAD speculated that the individuals participating in the inspection may not have been aware of how to retrieve the information. FDA acknowledged ARIAD’s response. FDA stated that the adequacy of the IRC data for inclusion in brigatinib product labeling would be determined upon FDA’s review of the submitted information. ARIAD expressed understanding and no further discussion occurred.

Clinical PMC
FDA requested clarification on whether patients participating in the ALTA trial be followed for 5 years. ARIAD confirmed; however, ARIAD stated that the proposed mature final data based on the study completion date of September 2017 would provide 2 years of follow-up. ARIAD acknowledged that analyses of any subsequent data cuts would be performed for non-regulatory purposes. FDA acknowledged ARIAD’s responses and stated that the proposed provision of 2 years of follow-up data is acceptable. FDA also stated that the proposed milestones were acceptable. FDA will provide ARIAD a simplified draft of proposed final PMC language for ARIAD’s formal agreement. ARIAD expressed understanding and no further discussion occurred.

Attachments:
- ARIAD’s 3/7/17, clinical PMC proposal
- ARIAD’s 3/8/17, IRC database source documentation proposal
- Tcon agenda provided on March 8, 2017
Hi Guilin,

The Team is requesting a teleconference with ARIAD to discuss the following two points:

1. ARIAD’s 3/1/17 response to our information request regarding the changes to the IRC database. Specifically, we are seeking access to source documentation supporting the information ARIAD has provided so that we can determine whether there is a path forward to verify this information.

2. Additionally, we would like to reach concurrence on the PMC for additional follow-up of Study 201 to better characterize the duration of intracranial response.

We are proposing **12:30 – 1:00 PM (EST) this Friday, March 10, 2017**. Can you please let me know as soon as possible whether this is conducive to your schedule? If acceptable, please provide us a TOLL-FREE teleconference number and passcode that can be used.

Please note that I will be sending you an IR shortly, regarding the IRC database changes.

Regards,

Leah S. Her, MS, PMP  
Regulatory Health Project Manager  
Division of Oncology Products 2 (DOP2)  
Food and Drug Administration  
10903 New Hampshire Avenue, Bldg 22, Room 2315  
Silver Spring, MD 20903  
Tel: 240-402-6611  
Fax: 301-796-9849  
Email: leah.her@fda.hhs.gov
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/s/

LEAH S HER
03/27/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We also refer to our January 9, 2017, carton and container labeling comments and request for information, and your response received on January 27, 2017, as a formal amendment to the NDA.

Upon additional review, we have the following request for information. Please provide your response via email as soon as possible but no later than Friday, March 31, 2017, and follow that with a formal submission to the NDA.

Comment:

1. Revise the order of information of the storage temperature language in the container and carton labeling, to state “Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59° to 86°F) (see USP).”

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
03/20/2017
Date: March 13, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

Proposed Post Marketing Commitment

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We propose the following Post Marketing Commitment (PMC). Please note that additional PMR and PMC proposals may be forthcoming while your application is under review. Please provide your agreement to the below proposal. Please provide a response as soon as possible but no later than 4 PM (EST), Friday, March 17, 2017.

POST MARKETING COMMITMENT

Clinical

1. Submit the final analysis of intracranial response duration based upon independent radiology reviewer assessment of imaging data collected for two years following the date of enrollment of the last patient in Study AP26113-13-201.

   The timetable you proposed and discussed during our March 10, 2017, teleconference is below:

   PMR/PMC Schedule
   Milestones:

   Study/Trial Completion: September 30, 2017
   Final Report Submission: March 31, 2018

   If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 4069115
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/s/

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LEAH S HER
03/13/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We also refer to our February 7, 2017, comments and request for information provided via an electronic mail (email) communication, and to your March 1, 2017, response submitted to the NDA.

The Clinical Reviewer has the following additional request for information. Please provide your response to via email as soon as possible, and follow that with a formal submission to the NDA.

Comments:

1. Please provide a list of people who initiated/authorized the IRC database changes. Include in your response, the following information:
   a. Name
   b. Title
   c. Affiliation
   d. Role in conduct of the study

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

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LEAH S HER
03/08/2017
MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 28, 2017
TIME: 1:30 - 2:00 PM (EST)
LOCATION: Teleconference
APPLICATION: NDA 208772
DRUG NAME: brigatinib

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Karen Arscott, D.O., M.Sc., AOBNMM, cleared for participation by CDER’s Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:
Martha Donoghue – Associate Director (Acting), DOP2
Steven Lemery – Clinical Team Leader, DOP2
Erin Larkins – Clinical Team Leader (Acting), DOP2
Naomi Horiba – Clinical Reviewer, DOP2
Leah Her – Regulatory Health Project Manager, DOP2

EXTERNAL CONSTITUENT ATTENDEES:
Karen Arscott, D.O., M.Sc., AOBNMM

BACKGROUND: Dr. Karen Arscott agreed to serve and was cleared as an SGE for this original NDA. Prior to this teleconference, background materials and draft product labeling were provided along with two specific questions from the Division for Dr. Arscott to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. As a treating physician or patient, would you be comfortable prescribing or receiving brigatinib for the treatment of ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib?

Discussion During Teleconference: Dr. Arscott commented on the list of adverse events noted with brigatinib in the briefing package and stated that these adverse events were similar to those of currently approved drugs with a similar mechanism of action. Dr. Arscott stated that the risks were acceptable based on the benefit seen with brigatinib. Dr. Arscott observed that brigatinib appeared to be a good option for patients who failed crizotinib and have no other alternatives.

Reference ID: 4065485
2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of brigatinib treatment?

**Discussion During Teleconference:** Dr. Arscott stated that label was clear.

Dr. Arscott had no further comments or questions.

**ATTACHMENTS:** Background information provided to Dr. Arscott via email (KArscott@tcme.edu) on February 13, 2017, which included:

- Briefing Document for FDA Teleconference to Discuss NDA 208772
- Draft Labeling of January 27, 2017
Karen Arscott, D.O., M.Sc., AOBNNM
The Commonwealth Medical College
525 Pine Street
Scranton, PA 18509

Dear Dr. Arscott:

We refer to the teleconference held on August 19, 2016, between yourself and Dr. Deborah Miller of the Office of Health and Constituent Affairs (OHCA), regarding the possibility of your assistance in the review of pending New Drug Application (NDA) 208772, submitted by ARIAD Pharmaceuticals Inc. Please note that information concerning this application is confidential.

In this application, ARIAD seeks approval of brigatinib (proposed as Alunbrig), for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

We have received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this pending NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for Tuesday, February 28, 2017 / 1:30 to 2:00 PM (EST). We will provide toll-free call in information in advance of this teleconference.

Enclosed is a summary of the single randomized trial submitted with this application, Study AP26113-13-201, and the proposed brigatinib product labeling for your review. The questions we would like to discuss during this teleconference are listed below; please let us know if you would like any additional information in order to aid in the discussion.

FDA Questions for Discussion During the Teleconference:

1. As a treating physician or patient, would you be comfortable prescribing or receiving brigatinib for the treatment of ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib?

2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of brigatinib treatment?

Thank you for your time and insights.
If you have questions, please contact me at 240-402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
1. NDA 208772 Summary Information
2. Draft brigatinib product labeling
3. Timekeeper Payroll Record
Briefing Document for FDA Teleconference to Discuss NDA 208772 – brigatinib tablets, for oral use
ARIAD Pharmaceuticals, Inc.

Protocol AP26113-13-201
A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib

Indication
For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Study Design
AP26113-13-201 (Trial ALTA) is a randomized, non-comparative, open-label, multicenter trial designed to evaluate the anti-tumor activity of brigatinib at two different doses in patients with ALK-positive NSCLC who have previously received crizotinib.

Patients were stratified according to brain metastases (present versus absent) and response to prior crizotinib (complete response [CR] or partial response [PR] vs other or unknown).

The primary objective was confirmed objective response rate (ORR) by investigator assessment.

Secondary objectives were as follows:
- Assess disease control rate (DCR), time to/duration of response, progression-free survival (PFS), overall survival (OS), and time on treatment
- Assess CNS response and PFS in patients who have active brain metastases
- Assess safety and tolerability of brigatinib in study patients
- Assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0).

Statistical considerations: There were no formal statistical hypotheses specified to assess treatment effects between the two arms. The primary analysis of ORR in the intention-to-treat (ITT) population was computation of exact 2-sided 97.5% binomial confidence intervals for each treatment arm. The study was designed to detect an alternative ORR of 35%; an ORR of 20% was considered uninteresting. A sample size of at least 218 patients (109 per arm) was determined to provide approximately 88% power to rule out an uninteresting response rate of 20% when the true rate was 35% or higher, with a two-sided alpha of 0.025 using an exact binomial test. The treatment regimen was considered to have achieved the primary objective when the ORR (investigator assessed) was shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at final analysis for the given regimen.
Patient Population

Key eligibility criteria:

- Age ≥ 18
- At least 1 measurable lesion per RECIST v1.1
- Histologically or cytologically confirmed locally advanced or metastatic NSCLC that is ALK+ by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or documented ALK positivity by a different test and tissue available for the Vysis® FISH test
- Progression of disease while on crizotinib; crizotinib need not have been the most recent therapy administered as of Amendment 2 (29 Jul 2014)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤ 450 ms in males or ≤ 470 ms in females
- Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤ 2

Key exclusion criteria:

- Any prior ALK-targeted TKI other than crizotinib
- Crizotinib within 3 days of the first dose of AP26113 (Day 1, Cycle 1)
- Cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except stereotactic radiosurgery
- Symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids

Treatment Regimen

Patients were randomized 1:1 to receive AP26113 in one of two different dosing regimens until progression or discontinuation for other reasons.

- Arm A (90 mg regimen): brigatinib 90 mg daily continuously
- Arm B (180 mg regimen): brigatinib 90 mg daily for 7 days, then 180 mg daily continuously

Patients in Arm A were permitted to cross over to Arm B upon progression. Disease assessments were performed every 8 weeks for 14 months then every 12 weeks.

Efficacy

A total of 222 patients were enrolled in 71 sites worldwide. Demographic and baseline disease characteristics and information regarding prior therapy are summarized in Tables 1-2.

<table>
<thead>
<tr>
<th>Table 1: Summary of Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Mean (SD) ^2</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

^1 Denotes formal randomization group assignment.

^2 Mean (SD) values are expressed as mean (standard deviation) in years.
<table>
<thead>
<tr>
<th></th>
<th>Arm A 90 mg regimen (N=112)</th>
<th>Arm B (n=110) 180 mg regimen (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>18-82</td>
<td>20-81</td>
</tr>
<tr>
<td><strong>≥ 65 years n (%)</strong></td>
<td>22 (20)</td>
<td>30 (27)</td>
</tr>
<tr>
<td><strong>Race n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 (64)</td>
<td>76 (69)</td>
</tr>
<tr>
<td>Asian</td>
<td>39 (35)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (55)</td>
<td>64 (58)</td>
</tr>
<tr>
<td>Male</td>
<td>50 (45)</td>
<td>46 (42)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (30)</td>
<td>45 (41)</td>
</tr>
<tr>
<td>1</td>
<td>71 (63)</td>
<td>56 (51)</td>
</tr>
<tr>
<td>2</td>
<td>7 (6)</td>
<td>9 (8)</td>
</tr>
<tr>
<td><strong>Smoking Status n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>71 (63)</td>
<td>63 (57)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>34 (30)</td>
<td>43 (39)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>6 (5)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

1 The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
2 SD standard deviation

**Table 2: Baseline Disease Characteristics for the ITT Population (Reviewer Table)**

<table>
<thead>
<tr>
<th></th>
<th>Arm A 90 mg regimen (N=112)</th>
<th>Arm B (n=110) 180 mg regimen (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK+ by Vysis FISH n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100 (89)</td>
<td>98 (89)</td>
</tr>
<tr>
<td>No</td>
<td>12 (11)</td>
<td>12 (11)</td>
</tr>
<tr>
<td><strong>Stage n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>IIIB</td>
<td>3 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>IV</td>
<td>109 (97)</td>
<td>108 (98)</td>
</tr>
<tr>
<td><strong>Histology n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>107 (96)</td>
<td>108 (98)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Squamous</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td><strong>CNS Metastases at Baseline n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 (71)</td>
<td>74 (67)</td>
</tr>
<tr>
<td><strong>Prior Platinum-based Chemotherapy n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83 (74)</td>
<td>80 (73)</td>
</tr>
<tr>
<td><strong>Prior Systemic Therapy (including crizotinib) n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 regimen (includes crizotinib)</td>
<td>29 (26)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>2 regimens (includes crizotinib)</td>
<td>40 (35.7)</td>
<td>45 (41)</td>
</tr>
</tbody>
</table>
### Table 1: Summary of Patient Disposition

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Arm A 90 mg QD N=112</th>
<th>Arm B 90 mg QD → 180 mg QD N=110</th>
<th>Total N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Patients, n (%)</td>
<td>109 (97.3)</td>
<td>110 (100.0)</td>
<td>219 (96.8)</td>
</tr>
<tr>
<td>Discontinued Patients, n (%)</td>
<td>45 (40.2)</td>
<td>34 (30.9)</td>
<td>79 (35.6)</td>
</tr>
<tr>
<td>Ongoing Patients, n (%)</td>
<td>64 (57.1)</td>
<td>76 (69.1)</td>
<td>140 (63.1)</td>
</tr>
<tr>
<td>Primary Reason for Treatment Discontinuation, n (%)</td>
<td>29 (25.9)</td>
<td>16 (14.5)</td>
<td>45 (20.3)</td>
</tr>
<tr>
<td>Clinical Progressive Disease, n (%)</td>
<td>4 (3.6)</td>
<td>3 (2.7)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Adverse Event, n (%)</td>
<td>3 (2.7)</td>
<td>9 (8.2)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>7 (6.3)</td>
<td>1 (0.9)</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Non-compliance with study drug, n (%)</td>
<td>0</td>
<td>1 (0.9)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Withdrawal by patient, n (%)</td>
<td>2 (1.8)</td>
<td>4 (3.6)</td>
<td>6 (2.7)</td>
</tr>
</tbody>
</table>

Source: Clinical Study Report Table 10-1

Efficacy results for response and duration of response (DoR) are summarized in Table 4.
Table 4: Results for Response and Duration of Response

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Arm A 90mg QD N=112</th>
<th>Arm B 90mg QD → 180 mg QD N=110</th>
<th>Total N=222</th>
<th>Arm A 90mg QD N=112</th>
<th>Arm B 90mg QD → 180 mg QD N=110</th>
<th>Total N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(%)</td>
<td>50 (44.6)</td>
<td>59 (53.6)</td>
<td>109 (49.1)</td>
<td>54 (48.2)</td>
<td>58 (52.7)</td>
<td>112 (50.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>35.2, 54.3</td>
<td>43.9, 63.2</td>
<td>42.4, 55.9</td>
<td>38.7, 57.9</td>
<td>43.0, 62.3</td>
<td>43.7, 57.2</td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.9)</td>
<td>4 (3.6)</td>
<td>5 (2.3)</td>
<td>4 (3.6)</td>
<td>5 (4.5)</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>PR</td>
<td>49 (43.8)</td>
<td>55 (50.0)</td>
<td>104 (46.8)</td>
<td>50 (44.6)</td>
<td>53 (48.2)</td>
<td>103 (46.4)</td>
</tr>
<tr>
<td>Duration of Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13.8</td>
<td>11.1</td>
<td>13.8</td>
<td>13.8</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>9.2, 13.8</td>
<td>9.9, 13.8</td>
<td>7.4, NE</td>
<td>9.3, NE</td>
<td>9.3, NE</td>
<td>9.3, NE</td>
</tr>
</tbody>
</table>

NE= Not Estimable
Source: Adapted from CSR Tables 11-1, 14.2.1.2, and 14.2.6.2

Efficacy results for intracranial metastases are summarized in Tables 5 (ORR in patients with any brain metastases at baseline) and Table 6 (ORR in patients with active brain metastases at baseline).

Table 5: IRC-Assessed Intracranial ORR in Patients with Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Patients with Measurable Brain Metastases</th>
<th>Patients with Only Nonmeasurable Brain Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A 90mg QD N=26</td>
<td>Arm B 90mg QD → 180 mg QD N=18</td>
</tr>
<tr>
<td>Confirmed IORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(%)</td>
<td>11 (42.3)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>23.4, 63.1</td>
<td>41.0, 86.7</td>
</tr>
<tr>
<td>CR</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>9 (34.6)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Duration of Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NE</td>
<td>5.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.7, NE</td>
<td>3.7, NE</td>
</tr>
</tbody>
</table>

NE= Not Estimable
Source: Adapted from CSR Table 11-2
Table 6: IRC-Assessed Intracranial ORR in Patients with *Active* Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Patients with Measurable Active Brain Metastases</th>
<th>Patients with Only Nonmeasurable Active Brain Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A 90mg QD N=19</td>
<td>Arm B 90mg QD → 180 mg QD N=15</td>
</tr>
<tr>
<td>Confirmed IORR</td>
<td>8 (42.1)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.3, 66.5</td>
<td>44.9, 92.2</td>
</tr>
<tr>
<td>CR</td>
<td>2 (10.5)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6 (31.6)</td>
<td>11 (73.3)</td>
</tr>
</tbody>
</table>

Duration of Response

<table>
<thead>
<tr>
<th>Median</th>
<th>Arm A 90mg QD N=32</th>
<th>Arm B 90mg QD → 180 mg QD N=36</th>
<th>Total N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>3.0, NE</td>
<td>3.7, NE</td>
<td>9.3, NE</td>
</tr>
</tbody>
</table>

*NE= Not Estimable*

Source: Adapted from CSR Tables 11-3, 14.2.5.2, 14.2.5.11

Although Trial ALTA was a non-comparative study and the analysis is exploratory, progression-free survival (PFS) is shown in Figure 1.

**Figure 1: Independent Review Committee (IRC)-Assessed Systemic PFS**

*Source: Clinical Study Report Fig. 11-6*

**Safety**

Median duration of treatment:

- Arm A (90 mg regimen): 9.8 months (range 0.3-20)
- Arm B (180 mg regimen): 10.7 months (range 0.07-23.6)

Relative dose intensity as calculated by the observed total dose divided by the expected total dose times 100. This number could exceed 100% if a patient crossed over to Arm B on progression:

- Arm A (90 mg regimen): 100% (range 65-192)
• Arm B (180 mg regimen): 99.5% (range 33-101)

The most significant toxicities related to brigatinib were:
• Early onset pulmonary events (EOPE)
• Hypertension
• CPK elevation
• Pancreatic enzyme elevation
• Hyperglycemia
• Bradycardia
• Vision disorders

Adverse events (AEs) leading to treatment discontinuation occurred in 2.8% of patients in Arm A and 8.2% in Arm B. The only AE leading to dose reduction that occurred in ≥2% of patients overall by preferred term was blood CPK increased, which occurred in 2 (1.8%) patients in Arm A and 5 (4.5%) patients in Arm B. The most common AEs that led to dose interruption in ALTA overall by preferred term were pneumonitis (9 [4.1%]), blood CPK increased (7 [3.2%]), lipase increased (7 [3.2%]), neoplasm progression (6 [2.7%]), and vomiting (6 [2.7%]). Dose interruptions due to pneumonitis all occurred at the 90 mg dose (i.e., Patients in Arm B were in the lead-in period and taking 90 mg daily).

The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in Arm A (15%) than Arm B (6%). Neoplasm progression was the most common cause of death in both arms. Four deaths overall were due to pulmonary events not related to disease progression (pneumonia, dyspnea, respiratory failure), and one sudden death occurred.

Among the 219 patients in Trial ALTA, 85 patients experienced 133 SAEs with similar rates in both arms (38% in Arm A and 40% in Arm B). The three most common SAEs by preferred term in Arm B were pneumonia (7%), pneumonitis (7%), and neoplasm progression (5.5%). In Arm A, neoplasm progression was the most common preferred term (12%) and the rates of pneumonia (2.8%) and pneumonitis (1.8%) were lower than in Arm B than Arm A.

Treatment emergent adverse events occurring in ≥10% (all grades) or ≥2% (Grade 3-4) of patients in Trial ALTA is summarized in Table 7.
Table 7: TEAEs Occurring in ≥10% (All Grades) or ≥2% (Grade 3-4) of Patients (n=219) in ALTA

<table>
<thead>
<tr>
<th>Preferred Term¹ Consolidated TEAE Category</th>
<th>Arm A: 90 mg regimen N=109</th>
<th>Arm B: 180 mg regimen² N=110</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grades 3-4 n (%)</td>
</tr>
<tr>
<td>Patients with any TEAE</td>
<td>106 (97)</td>
<td>44 (40)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (33)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (29)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Blood Creatine Phosphokinase Increased</td>
<td>12 (11)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>30 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (24)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23 (21)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (11)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>13 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (10)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21 (19)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 (22)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increased</td>
<td>9 (8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Amylase Increased</td>
<td>9 (8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (14)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Lipase Increased</td>
<td>8 (7.3)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (4.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (2.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (5.5)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Neoplasm Progression</td>
<td>13 (12)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>12 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>AESI or SMQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease SMQ (narrow)⁷</td>
<td>4 (2.1)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Bradycardia⁸</td>
<td>6 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (11)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Visual Disturbance⁹</td>
<td>4 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia¹⁰</td>
<td>10 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Patients may have more than one AE per preferred term. A patient is counted once for the most severe event per preferred term.
² The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
There were no Grade 4 events for this preferred term.

The preferred terms fatigue and asthenia were combined.

All preferred terms including the word “rash” were included (e.g. rash macular, rash erythematous, rash pruritic)

The preferred terms neutropenia and neutrophil count decreased were combined.

The preferred terms pneumonitis and interstitial lung disease are represented from Interstitial Lung Disease SMQ narrow.

The preferred terms bradycardia and sinus bradycardia were combined.

The preferred terms visual acuity reduced, vision blurred, diplopia, visual impairment, and macular edema were combined.

The preferred terms myalgia and musculoskeletal pain were combined. There was no preferred term of rhabdomyolysis in the dataset.

An early onset pulmonary event (EOPE) led to one possible death in Trial ALTA (pneumonia), and 14 (6.4%) patients overall had an EOPE event that was at least possibly related to brigatinib, all occurring at the 90 mg dose level. EOPE led to dose discontinuations in 5 (2.3%) patients and drug interruption usually led to recovery. Seven of 14 (7/14) patients discontinued brigatinib permanently. In the other 7 patients, 6 had dose interruption of brigatinib and supportive care (antibiotics, steroids, supplemental oxygen, or a combination of these) with resolution of the pulmonary events. These patients were able to resume brigatinib. One patient continued brigatinib and the event resolved without dose modification.

Hypertension AEs of any grade occurred in 35 (16%) of patients overall and in a greater proportion of patients in Arm B than in Arm A (21% [23] vs 11 [12%], respectively). Hypertension Grade ≥3 occurred in 5.6 (5.5%) of patients in Arm A and 7 (6.4%) of patients in Arm B. Hypertension led to brigatinib dose interruptions in 2 patients (1.8%) in Arm B and none in Arm A. One patient in Arm B had a dose reduction and there were no discontinuations due to a hypertension event. Ariad included hypertension as a Warning in product labeling.

In Trial ALTA, amylase elevations occurred in 27% of patients in the 90 mg regimen and 39% of patients in the 180 mg regimen. Lipase evaluations occurred in 21% of patients in the 90 mg regimen and 45% of patients in the 180 mg regimen. Grade 3-4 pancreatic enzyme elevation took place in 3.7% of patients in the 90 mg regimen and 2.7% of patients in the 180 mg regimen. There were no clinical pancreatitis AEs in Trial ALTA. Pancreatic events of increased lipase and increased amylase led to a brigatinib dose interruption in 7 [3.2%] and 3 (1.4%) patients respectively. Increased lipase led to brigatinib dose reduction in 2 (0.9%) patients (one in each arm) and increased amylase in 1 (0.5%) patient. No patients discontinued brigatinib due to a pancreatic event.

CPK laboratory elevations of any grade and Grade ≥3 were more common in Arm B than in Arm A (any grade: 48.2% vs 26.6%, respectively; Grade 3 or 4: 11.8% vs 2.8%, respectively). AEs of increased CPK levels led to dose interruption in more patients in Arm B than in Arm A (5.5% vs 0.9%, respectively) and similarly to dose reduction in more patients in Arm B than in Arm A (4.5% vs 1.8%, respectively).

Elevated insulin/hyperglycemia events of any grade occurred in 12 (5.5%) patients overall. More events took place in Arm B (10 [9%] patients) than Arm A (2 [1.8%] patients). A Grade ≥3 event of diabetes mellitus occurred in one patient in Arm B who did not have a pre-existing diagnosis of

Reference ID: 4065485
diabetes. Hyperglycemia events led to dose interruption in one patient. No dose reduction or discontinuation due to elevated insulin/hyperglycemia events took place.

Bradycardia is a class effect of ALK-inhibitor TKIs. Based on review of patients with at least one post-baseline ECG, 6 of 106 patients in Arm A (5.7%) and 8 of 105 patients in Arm B (7.6%) with at least one post-baseline ECG had bradycardia defined as less than 50 beats per minute.

Bradycardia was reported as an AE in 10 (4.6%) of patients overall, and was symptomatic in one patient (Grade 2). No Grade 3 or greater bradycardia was reported. There were no brigatinib dose interruptions, dose reductions, or dose discontinuations due to bradycardia events.

Vision disorders have been reported in other ALK-inhibitor TKIs. Vision disorder events of any grade occurred in 9 (8%) patients in Arm A and 16 (15%) patients in Arm B. The most common preferred term was vision blurred which occurred in a similar proportion of patients in both arms (3 [2.8%] patients overall). There was a single Grade 3 event of macular edema that resolved with interruption of 1 month. Brigatinib was restarted at a lower dose, and Grade 2 macular edema was reported and did not abate with interruption.

Summary

Two marketed orally-administered tyrosine kinase inhibitors (TKIs) for metastatic ALK-positive NSCLC, ceritinib and alectinib, received accelerated approval in 2014 and 2015, respectively. These drugs are not considered available therapy as defined in FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics, because they have not received regular approval. FDA is considering the overall risk-benefit profile of brigatinib in the context of lack of available therapy and life-threatening nature of metastatic NSCLC. ARIAD’s application for brigatinib is being considered under the accelerated approval pathway and FDA is assessing whether the clinical effects on ORR, intracranial response, and DoR are reasonably likely to predict clinical benefit in patients with ALK-fusion lung cancer who have previously received crizotinib. ARIAD is currently conducting a randomized trial of brigatinib versus crizotinib for patients with ALK-positive NSCLC who have received no more than one line of chemotherapy (excluding TKIs) with a primary endpoint of PFS; ARIAD intends this study to serve as the confirmatory trial for regular approval.

Based on Trial ALTA, brigatinib appears to confer a clinically meaningful improvement in ORR and DoR as compared to historical control. Intracranial response rate, a secondary endpoint, appears to be promising. Due to the absence of a control arm in Trial ALTA, however, residual uncertainty exists as to the safety profile and contribution of brigatinib to some of the adverse events in a patient population with late stage lung cancer. Nonetheless, some of the apparent toxicities have been seen with other drugs in this class, with notable exceptions being early onset pulmonary events and hypertension. Overall, brigatinib therapy appears to show a meaningful clinical improvement in patients with ALK-positive NSCLC whose disease has progressed on crizotinib, with a manageable toxicity profile.
TIMEKEEPER PAYROLL RECORD
Advisors and Consultants Staff

Note to Center for Drug Evaluation and Research Special Government Employee.
Use this record to submit claim for hours worked at your home, place of business, or in any FDA facility located within your commuting area. Please note any dates that you were required to travel outside of your commuting area to perform your assignment. Advisory committee members should not claim salary for hours spent on normal preparation for a committee meeting. Salary paid in response to this time sheet represents compensation in full for all services rendered and supplied by the Special Government Employee during this period.

<table>
<thead>
<tr>
<th>Date(s)</th>
<th>Hours Worked</th>
<th>Description of Work</th>
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<tr>
<td></td>
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<td>(Cite IND/NDA if applicable)</td>
</tr>
</tbody>
</table>

(Sign)  __________________________  __________________________
Special Government Employee  Date

Certification:
I certify that this work was done during the period(s) indicated at:

☐ Government furnished facility
☐ Employees home/office since there was no Federal office or laboratory space available at which to perform the assigned work.
☐ Quality and quantity of work meets performance expectations.

______________________________  __________________________
Center for Drug Evaluation and Research Executive  Date
Secretary/Management Official Authorizing Assignment
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH S HER
03/06/2017
MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 28, 2017
TIME: 2:00 - 2:30 PM (EST)
LOCATION: Teleconference
APPLICATION: NDA 208772
DRUG NAME: brigatinib
TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Eva Szabo, M.D., cleared for participation by CDER’s Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:
Martha Donoghue – Associate Director (Acting), DOP2
Steven Lemery – Clinical Team Leader, DOP2
Erin Larkins – Clinical Team Leader (Acting), DOP2
Naomi Horiba – Clinical Reviewer, DOP2
Leah Her – Regulatory Health Project Manager, DOP2

EXTERNAL CONSTITUENT ATTENDEES:
Eva Szabo, M.D.

BACKGROUND: Dr. Eva Szabo agreed to serve and was cleared as an SGE for this original NDA. Prior to this teleconference, background materials and draft product labeling were provided along with two specific questions from the Division for Dr. Szabo to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. As a treating physician or patient, would you be comfortable prescribing or receiving brigatinib for the treatment of ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib?

   Discussion During Teleconference: Dr. Szabo stated that the trial appeared to have been well conducted with a clear outcome demonstrating that brigatinib was efficacious in the intended population. She stated that most of the toxicities appeared manageable. Dr. Szabo stated that the presented data demonstrated a favorable risk-benefit ratio.
2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of brigatinib treatment?

**Discussion During Teleconference:** Dr. Szabo stated that the label overall was clear. Dr. Szabo observed some minor inconsistencies in the package insert and patient information and provided examples for FDA’s consideration. FDA agreed, and informed her that language for the label is still being written.

Dr. Szabo had no further comments or questions.

**ATTACHMENTS:** Background information provided to Dr. Szabo via email (szaboe@mail.nih.gov) on February 13, 2017, which included:

- Briefing Document for FDA Teleconference to Discuss NDA 208772
- Draft Labeling of January 27, 2017
Eva Szabo, M.D.
National Cancer Institute
9609 Medical Center Drive, Room 5E-102
Bethesda, MD 20892

Dear Dr. Szabo:

We refer to the teleconference held on November 18, 2016, between yourself and Drs. Steven Lemery and Naomi Horiba of the Division of Oncology Products 2 (DOP2), regarding the possibility of your assistance in the review of pending New Drug Application (NDA) 208772, submitted by ARIAD Pharmaceuticals Inc. Please note that information concerning this application is confidential.

In this application, ARIAD seeks approval of brigatinib (proposed as Alunbrig), for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

We have received notification from the CDER Division of Advisory Committee and Consultant Management (DACCMM) that you are cleared to serve as a Special Government Employee (SGE) for the review of this pending NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for Tuesday, February 28, 2017 / 2:00 to 2:30 PM (EST). We will provide toll-free call in information in advance of this teleconference.

Enclosed is a summary of the single randomized trial submitted with this application, Study AP26113-13-201, and the proposed brigatinib product labeling for your review. The questions we would like to discuss during this teleconference are listed below; please let us know if you would like any additional information in order to aid in the discussion.

**FDA Questions for Discussion During the Teleconference:**

1. As a treating physician or patient, would you be comfortable prescribing or receiving brigatinib for the treatment of ALK-positive NSCLC in patients who have progressed on or are intolerant to crizotinib?

2. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of brigatinib treatment?

Thank you for your time and insights.

Reference ID: 4065486
If you have questions, please contact me at 240-402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
1. NDA 208772 Summary Information
2. Draft brigatinib product labeling
Briefing Document for FDA Teleconference to Discuss NDA 208772 – brigatinib tablets, for oral use
ARIAD Pharmaceuticals, Inc.

Protocol AP26113-13-201
A Randomized Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib

Indication
For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Study Design
AP26113-13-201 (Trial ALTA) is a randomized, non-comparative, open-label, multicenter trial designed to evaluate the anti-tumor activity of brigatinib at two different doses in patients with ALK-positive NSCLC who have previously received crizotinib.

Patients were stratified according to brain metastases (present versus absent) and response to prior crizotinib (complete response [CR] or partial response [PR] vs other or unknown).

The primary objective was confirmed objective response rate (ORR) by investigator assessment.

Secondary objectives were as follows:
- Assess disease control rate (DCR), time to/duration of response, progression-free survival (PFS), overall survival (OS), and time on treatment
- Assess CNS response and PFS in patients who have active brain metastases
- Assess safety and tolerability of brigatinib in study patients
- Assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0).

Statistical considerations: There were no formal statistical hypotheses specified to assess treatment effects between the two arms. The primary analysis of ORR in the intention-to-treat (ITT) population was computation of exact 2-sided 97.5% binomial confidence intervals for each treatment arm. The study was designed to detect an alternative ORR of 35%; an ORR of 20% was considered uninteresting. A sample size of at least 218 patients (109 per arm) was determined to provide approximately 88% power to rule out an uninteresting response rate of 20% when the true rate was 35% or higher, with a two-sided alpha of 0.025 using an exact binomial test. The treatment regimen was considered to have achieved the primary objective when the ORR (investigator assessed) was shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at final analysis for the given regimen.
Patient Population
Key eligibility criteria:

- Age ≥18
- At least 1 measurable lesion per RECIST v1.1
- Histologically or cytologically confirmed locally advanced or metastatic NSCLC that is ALK+ by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or documented ALK positivity by a different test and tissue available for the Vysis® FISH test
- Progression of disease while on crizotinib; crizotinib need not have been the most recent therapy administered as of Amendment 2 (29 Jul 2014)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Normal QT interval on screening electrocardiogram (ECG) evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤450 ms in males or ≤470 ms in females
- Recovered from toxicities related to prior anticancer therapy to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v4.0) grade ≤2

Key exclusion criteria:

- Any prior ALK-targeted TKI other than crizotinib
- Crizotinib within 3 days of the first dose of AP26113 (Day 1, Cycle 1)
- Cytotoxic chemotherapy, investigational agents, or radiation within 14 days, except stereotactic radiosurgery
- Symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids

Treatment Regimen
Patients were randomized 1:1 to receive AP26113 in one of two different dosing regimens until progression or discontinuation for other reasons.

- Arm A (90 mg regimen): brigatinib 90 mg daily continuously
- Arm B (180 mg regimen): brigatinib 90 mg daily for 7 days, then 180 mg daily continuously

Patients in Arm A were permitted to cross over to Arm B upon progression. Disease assessments were performed every 8 weeks for 14 months then every 12 weeks.

Efficacy
A total of 222 patients were enrolled in 71 sites worldwide. Demographic and baseline disease characteristics and information regarding prior therapy are summarized in Tables 1-2.

Table 1: Summary of Demographics

<table>
<thead>
<tr>
<th></th>
<th>Arm A 90 mg regimen (n=112)</th>
<th>Arm B 180 mg regimen (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>52 (13)</td>
<td>56 (13)</td>
</tr>
<tr>
<td></td>
<td>Arm A 90 mg regimen (N=112) n (%)</td>
<td>Arm B (n=110) 180 mg regimen (N=110) n (%)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>18-82</td>
<td>20-81</td>
</tr>
<tr>
<td><strong>≥ 65 years n (%)</strong></td>
<td>22 (20)</td>
<td>30 (27)</td>
</tr>
<tr>
<td><strong>Race n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 (64)</td>
<td>76 (69)</td>
</tr>
<tr>
<td>Asian</td>
<td>39 (35)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (55)</td>
<td>64 (58)</td>
</tr>
<tr>
<td>Male</td>
<td>50 (45)</td>
<td>46 (42)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34 (30)</td>
<td>45 (41)</td>
</tr>
<tr>
<td>1</td>
<td>71 (63)</td>
<td>56 (51)</td>
</tr>
<tr>
<td>2</td>
<td>7 (6)</td>
<td>9 (8)</td>
</tr>
<tr>
<td><strong>Smoking Status n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>71 (63)</td>
<td>63 (57)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>34 (30)</td>
<td>43 (39)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>6 (5)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

1 The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.  
2 SD standard deviation

**Table 2: Baseline Disease Characteristics for the ITT Population (Reviewer Table)**

<table>
<thead>
<tr>
<th>ALK+ by Vysis FISH n (%)</th>
<th>Arm A 90 mg regimen (N=112) n (%)</th>
<th>Arm B (n=110) 180 mg regimen (N=110) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>100 (89)</td>
<td>98 (89)</td>
</tr>
<tr>
<td>No³</td>
<td>12 (11)</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage n (%)</th>
<th>Arm A 90 mg regimen (N=112) n (%)</th>
<th>Arm B (n=110) 180 mg regimen (N=110) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>IIIB</td>
<td>3 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>IV</td>
<td>109 (97)</td>
<td>108 (98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology n (%)</th>
<th>Arm A 90 mg regimen (N=112) n (%)</th>
<th>Arm B (n=110) 180 mg regimen (N=110) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>107 (96)</td>
<td>108 (98)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Squamous</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Other⁴</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>CNS Metastases at Baseline n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Platinum-based Chemotherapy n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Systemic Therapy (including crizotinib) n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 regimen (includes crizotinib)</td>
<td>29 (26)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>2 regimens (includes crizotinib)</td>
<td>40 (35.7)</td>
<td>45 (41)</td>
</tr>
</tbody>
</table>
≥3 regimens (includes crizotinib) | 43 (38) | 38 (35)
---|---|---
**Prior radiotherapy n (%)**
Prior radiotherapy (to any site) | 68 (61) | 58 (53)
Radiotherapy for brain metastasis | 50 (45) | 45 (41)
**Most Recent Systemic Therapy was crizotinib n (%)** | 107 (96) | 106 (96)
Complete Response | 5 (4.5) | 2 (1.8)
Partial Response | 65 (58) | 70 (64)
Stable Disease | 28 (25.) | 21 (19)
Progressive Disease | 8 (7) | 6 (5.5)
Other/Unknown | 6 (5.4) | 11 (10)

1 ITT population contains 3 patients who are not included in the safety population in Arm A because they did not receive therapy.
2 The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
3 Of the 24 patients without a positive local or central ALK Vysis FISH (versus a different) test result, no central test result was listed due to insufficient tissue (n=6); improper tissue preparation (n=12); or central test negative (n=5); central test abnormal – loss of 3’ ALK signal (n=1).
4 Large cell and mucoeidermoid carcinoma
5 “Other” denotes 2 patients (one in each arm) for whom PR or better was achieved but unable to classify as PR or CR. “Unknown” denotes the remaining patients for whom the best response to crizotinib was unavailable. Of note, all patients ultimately had progression of disease on crizotinib prior to enrollment.

Patient disposition is summarized in Table 3.

**Table 3: Summary of Patient Disposition**

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Arm A 90 mg QD N=112</th>
<th>Arm B 90 mg QD →180 mg QD N=110</th>
<th>Total N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Patients, n (%)</td>
<td>109 (97 3)</td>
<td>110 (100 0)</td>
<td>219 (98 6)</td>
</tr>
<tr>
<td>Discontinued Patients, n (%)</td>
<td>45 (40 2)</td>
<td>34 (30 9)</td>
<td>79 (35 6)</td>
</tr>
<tr>
<td>Ongoing Patients, n (%)</td>
<td>64 (57 1)</td>
<td>76 (69 1)</td>
<td>140 (63 1)</td>
</tr>
<tr>
<td>Primary Reason for Treatment Discontinuation n (%)</td>
<td></td>
<td></td>
<td>45 (20 3)</td>
</tr>
<tr>
<td>Clinical Progressive Disease, n (%)</td>
<td>4 (3 6)</td>
<td>3 (2 7)</td>
<td>7 (3 2)</td>
</tr>
<tr>
<td>Adverse Event, n (%)</td>
<td>3 (2 7)</td>
<td>9 (8 2)</td>
<td>12 (5 4)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>7 (6 3)</td>
<td>1 (0 9)</td>
<td>8 (3 6)</td>
</tr>
<tr>
<td>Non-compliance with study drug, n (%)</td>
<td>0</td>
<td>1 (0 9)</td>
<td>1 (0 5)</td>
</tr>
<tr>
<td>Withdrawal by patient, n (%)</td>
<td>2 (1 8)</td>
<td>4 (3 6)</td>
<td>6 (2 7)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>112</td>
<td>110</td>
<td>222</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7 97 (4 078)</td>
<td>8 91 (3 984)</td>
<td>8 43 (4 050)</td>
</tr>
<tr>
<td>Median</td>
<td>7 75</td>
<td>8 26</td>
<td>7 97</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0 1, 16 7</td>
<td>0 1, 20 2</td>
<td>0 1, 20 2</td>
</tr>
</tbody>
</table>

Source: Clinical Study Report Table 10-1

Efficacy results for response and duration of response (DoR) are summarized in Table 4.
### Table 4: Results for Response and Duration of Response

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Arm A 90mg QD N=112</th>
<th>Arm B 90mg QD → 180 mg QD N=110</th>
<th>Total N=222</th>
<th>Arm A 90mg QD N=112</th>
<th>Arm B 90mg QD → 180 mg QD N=110</th>
<th>Total N=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>50 (44.6%)</td>
<td>59 (53.6%)</td>
<td>109 (49.1%)</td>
<td>54 (48.2%)</td>
<td>58 (52.7%)</td>
<td>112 (50.5%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>35.2, 54.3</td>
<td>43.9, 63.2</td>
<td>42.4, 55.9</td>
<td>38.7, 57.9</td>
<td>43.0, 62.3</td>
<td>43.7, 57.2</td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.9%)</td>
<td>4 (3.6%)</td>
<td>5 (2.3%)</td>
<td>4 (3.6%)</td>
<td>5 (4.5%)</td>
<td>9 (4.1%)</td>
</tr>
<tr>
<td>PR</td>
<td>49 (43.8%)</td>
<td>55 (50.0%)</td>
<td>104 (46.8%)</td>
<td>50 (44.6%)</td>
<td>53 (48.2%)</td>
<td>103 (46.4%)</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>Median</td>
<td>13.8</td>
<td>11.1</td>
<td>13.8</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.4, NE</td>
<td>9.2, 13.8</td>
<td>9.9, 13.8</td>
<td>7.4, NE</td>
<td>9.5, NE</td>
<td>9.3, NE</td>
</tr>
</tbody>
</table>

NE= Not Estimable

Source: Adapted from CSR Tables 11-1, 14.2.1.2, and 14.2.6.2

Efficacy results for intracranial metastases are summarized in Tables 5 (ORR in patients with any brain metastases at baseline) and Table 6 (ORR in patients with *active* brain metastases at baseline).

### Table 5: IRC-Assessed Intracranial ORR in Patients with Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Arm A 90mg QD N=26</th>
<th>Arm B 90mg QD → 180 mg QD N=18</th>
<th>Total N=44</th>
<th>Arm A 90mg QD N=54</th>
<th>Arm B 90mg QD → 180 mg QD N=55</th>
<th>Total N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed IORR</td>
<td>11 (42.3%)</td>
<td>12 (66.7%)</td>
<td>23 (52.3%)</td>
<td>4 (7.4%)</td>
<td>10 (18.2%)</td>
<td>14 (12.8%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>23.4, 63.1</td>
<td>41.0, 86.7</td>
<td>36.7, 67.5</td>
<td>23.1, 37.9</td>
<td>9.1, 30.9</td>
<td>7.2, 20.6</td>
</tr>
<tr>
<td>CR</td>
<td>2 (7.7%)</td>
<td>0</td>
<td>2 (4.5%)</td>
<td>4 (7.4%)</td>
<td>10 (18.2%)</td>
<td>14 (12.8%)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (34.6%)</td>
<td>12 (66.7%)</td>
<td>21 (47.7%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>Median</td>
<td>5.6</td>
<td>5.6</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.7, NE</td>
<td>3.7, NE</td>
<td>3.9, NE</td>
<td>NE, NE</td>
<td>9.3, NE</td>
<td>9.3, NE</td>
</tr>
</tbody>
</table>

NE= Not Estimable

Source: Adapted from CSR Table 11-2
Table 6: IRC-Assessed Intracranial ORR in Patients with *Active* Brain Metastases at Baseline

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Patients with Measurable Active Brain Metastases</th>
<th>Patients with Only Nonmeasurable Active Brain Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A 90mg QD N=19</td>
<td>Arm B 90mg QD -&gt; 180 mg QD N=15</td>
</tr>
<tr>
<td>Confirmed IORR n(%)</td>
<td>8 (42.1)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.3, 66.5</td>
<td>44.9, 92.2</td>
</tr>
<tr>
<td>CR</td>
<td>2 (10.5)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6 (31.6)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>Median</td>
<td>5.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.7, NE</td>
<td>3.0, NE</td>
</tr>
</tbody>
</table>

*NE* = Not Estimable
Source: Adapted from CSR Tables 11-3, 14.2.5.2, 14.2.5.11

Although Trial ALTA was a non-comparative study and the analysis is exploratory, progression-free survival (PFS) is shown in Figure 1.

**Figure 1: Independent Review Committee (IRC)-Assessed Systemic PFS**

![Figure 1: Independent Review Committee (IRC)-Assessed Systemic PFS](source: Clinical Study Report Fig. 11-6)

**Safety**

Median duration of treatment:
- Arm A (90 mg regimen): 9.8 months (range 0.3-20)
- Arm B (180 mg regimen): 10.7 months (range 0.07-23.6)

Relative dose intensity as calculated by the observed total dose divided by the expected total dose times 100. This number could exceed 100% in Arm A if a patient crossed over to Arm B on progression:
- Arm A (90 mg regimen): 100% (range 65-192)
- Arm B (180 mg regimen): 99.5% (range 33-101)

The most significant toxicities related to brigatinib were:
- Early onset pulmonary events (EOPE)
- Hypertension
- CPK elevation
- Pancreatic enzyme elevation
- Hyperglycemia
- Bradycardia
- Vision disorders

Adverse events (AEs) leading to treatment discontinuation occurred in 2.8% of patients in Arm A and 8.2% in Arm B. The only AE leading to dose reduction that occurred in ≥2% of patients overall by preferred term was blood CPK increased, which occurred in 2 (1.8%) patients in Arm A and 5 (4.5%) patients in Arm B. The most common AEs that led to dose interruption in ALTA overall by preferred term were pneumonitis (9 [4.1%]), blood CPK increased (7 [3.2%]), lipase increased (7 [3.2%]), neoplasm progression (6 [2.7%]), and vomiting (6 [2.7%]). Dose interruptions due to pneumonitis all occurred at the 90 mg dose (i.e., Patients in Arm B were in the lead-in period and taking 90 mg daily).

The proportion of deaths that occurred within 30 days of the last dose of treatment was higher in Arm A (15%) than Arm B (6%). Neoplasm progression was the most common cause of death in both arms. Four deaths overall were due to pulmonary events not related to disease progression (pneumonia, dyspnea, respiratory failure), and one sudden death occurred.

Among the 219 patients in Trial ALTA, 85 patients experienced 133 SAEs with similar rates in both arms (38% in Arm A and 40% in Arm B). The three most common SAEs by preferred term in Arm B were pneumonia (7%), pneumonitis (7%), and neoplasm progression (5.5%). In Arm A, neoplasm progression was the most common preferred term (12%) and the rates of pneumonia (2.8%) and pneumonitis (1.8%) were lower than in Arm B than Arm A.

Treatment emergent adverse events occurring in ≥10% (all grades) or ≥2% (Grade 3-4) of patients in Trial ALTA is summarized in Table 7.
Table 7: TEAEs Occurring in ≥10% (All Grades) or ≥2% (Grade 3-4) of Patients (n=219) in ALTA

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Arm A: 90 mg regimen N=109</th>
<th>Arm B: 180 mg regimen N=110</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grades 3-4 n (%)</td>
</tr>
<tr>
<td><strong>Patients with any TEAE</strong></td>
<td>106 (97)</td>
<td>44 (40)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36 (33)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (29)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Blood Creatine Phosphokinase Increased</td>
<td>12 (11)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>30 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (24)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23 (21)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (11)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>13 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (10)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21 (19)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 (22)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increased</td>
<td>9 (8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Amylase Increased</td>
<td>9 (8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Articulargia</td>
<td>15 (14)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Lipase Increased</td>
<td>8 (7.3)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (4.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (5.5)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Neoplasm Progression</td>
<td>13 (12)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>12 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td><strong>AESI or SMQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease SMQ (narrow)</td>
<td>4</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (11)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Visual Disturbance</td>
<td>4 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Patients may have more than one AE per preferred term. A patient is counted once for the most severe event per preferred term.

2 The 180 mg regimen includes dosing at 90 mg daily for 7 days prior to escalation to 180 mg daily.
3 There were no Grade 4 events for this preferred term. 
4 The preferred terms fatigue and asthenia were combined. 
5 All preferred terms including the word “rash” were included (e.g. rash macular, rash erythematous, rash pruritic) 
6 The preferred terms neutropenia and neutrophil count decreased were combined. 
7 The preferred terms pneumonitis and interstitial lung disease are represented from Interstitial Lung Disease SMQ narrow. 
8 The preferred terms bradycardia and sinus bradycardia were combined. 
9 The preferred terms visual acuity reduced, vision blurred, diplopia, visual impairment, and macular edema were combined. 
10 The preferred terms myalgia and musculoskeletal pain were combined. There was no preferred term of rhabdomyolysis in the dataset.

An early onset pulmonary event (EOPE) led to one possible death in Trial ALTA (pneumonia), and 14 (6.4%) patients overall had an EOPE event that was at least possibly related to brigatinib, all occurring at the 90 mg dose level. EOPE led to dose discontinuations in 5 (2.3%) patients and drug interruption usually led to recovery. Seven of 14 (7/14) patients discontinued brigatinib permanently. In the other 7 patients, 6 had dose interruption of brigatinib and supportive care (antibiotics, steroids, supplemental oxygen, or a combination of these) with resolution of the pulmonary events. These patients were able to resume brigatinib. One patient continued brigatinib and the event resolved without dose modification.

Hypertension AEs of any grade occurred in 35 (16%) of patients overall and in a greater proportion of patients in Arm B than in Arm A (21% [23] vs 11 [12%], respectively). Hypertension Grade ≥3 occurred in 5.6 (5.5%) of patients in Arm A and 7 (6.4%) of patients in Arm B. Hypertension led to brigatinib dose interruptions in 2 patients (1.8%) in Arm B and none in Arm A. One patient in Arm B had a dose reduction and there were no discontinuations due to a hypertension event. Ariad included hypertension as a Warning in product labeling.

In Trial ALTA, amylase elevations occurred in 27% of patients in the 90 mg regimen and 39% of patients in the 180 mg regimen. Lipase evaluations occurred in 21% of patients in the 90 mg regimen and 45% of patients in the 180 mg regimen. Grade 3-4 pancreatic enzyme elevation took place in 3.7% of patients in the 90 mg regimen and 2.7% of patients in the 180 mg regimen. There were no clinical pancreatitis AEs in Trial ALTA. Pancreatic events of increased lipase and increased amylase led to a brigatinib dose interruption in 7 [3.2%] and 3 (1.4%) patients respectively. Increased lipase led to brigatinib dose reduction in 2 (0.9%) patients (one in each arm) and increased amylase in 1 (0.5%) patient. No patients discontinued brigatinib due to a pancreatic event.

CPK laboratory elevations of any grade and Grade ≥3 were more common in Arm B than in Arm A (any grade: 48.2% vs 26.6%, respectively; Grade 3 or 4: 11.8% vs 2.8%, respectively). AEs of increased CPK levels led to dose interruption in more patients in Arm B than in Arm A (5.5% vs 0.9%, respectively) and similarly to dose reduction in more patients in Arm B than in Arm A (4.5% vs 1.8%, respectively).

Elevated insulin/hyperglycemia events of any grade occurred in 12 (5.5%) patients overall. More events took place in Arm B (10 [9%] patients) than Arm A (2 [1.8%] patients). A Grade ≥3 event of diabetes mellitus occurred in one patient in Arm B who did not have a pre-existing diagnosis of diabetes.
diabetes. Hyperglycemia events led to dose interruption in one patient. No dose reduction or discontinuation due to elevated insulin/hyperglycemia events took place.

Bradycardia is a class effect of ALK-inhibitor TKIs. Based on review of patients with at least one post-baseline ECG, 6 of 106 patients in Arm A (5.7%) and 8 of 105 patients in Arm B (7.6%) with at least one post-baseline ECG had bradycardia defined as less than 50 beats per minute.

Bradycardia was reported as an AE in 10 (4.6%) of patients overall, and was symptomatic in one patient (Grade 2). No Grade 3 or greater bradycardia was reported. There were no brigatinib dose interruptions, dose reductions, or dose discontinuations due to bradycardia events.

Vision disorders have been reported in other ALK-inhibitor TKIs. Vision disorder events of any grade occurred in 9 (8%) patients in Arm A and 16 (15%) patients in Arm B. The most common preferred term was vision blurred which occurred in a similar proportion of patients in both arms (3 [2.8%] patients overall). There was a single Grade 3 event of macular edema that resolved with interruption of 1 month. Brigatinib was restarted at a lower dose, and Grade 2 macular edema was reported and did not abate with interruption.

Summary
Two marketed orally-administered tyrosine kinase inhibitors (TKIs) for metastatic ALK-positive NSCLC, ceritinib and alectinib, received accelerated approval in 2014 and 2015, respectively. These drugs are not considered available therapy as defined in FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics, because they have not received regular approval. FDA is considering the overall risk-benefit profile of brigatinib in the context of lack of available therapy and life-threatening nature of metastatic NSCLC. ARIAD’s application for brigatinib is being considered under the accelerated approval pathway and FDA is assessing whether the clinical effects on ORR, intracranial response, and DoR are reasonably likely to predict clinical benefit in patients with ALK-fusion lung cancer who have previously received crizotinib. ARIAD is currently conducting a randomized trial of brigatinib versus crizotinib for patients with ALK-positive NSCLC who have received no more than one line of chemotherapy (excluding TKIs) with a primary endpoint of PFS; ARIAD intends this study to serve as the confirmatory trial for regular approval.

Based on Trial ALTA, brigatinib appears to confer a clinically meaningful improvement in ORR and DoR as compared to historical control. Intracranial response rate, a secondary endpoint, appears to be promising. Due to the absence of a control arm in Trial ALTA, however, residual uncertainty exists as to the safety profile and contribution of brigatinib to some of the adverse events in a patient population with late stage lung cancer. Nonetheless, some of the apparent toxicities have been seen with other drugs in this class, with notable exceptions being early onset pulmonary events and hypertension. Overall, brigatinib therapy appears to show a meaningful clinical improvement in patients with ALK-positive NSCLC whose disease has progressed on crizotinib, with a manageable toxicity profile.

Reference ID: 4065486
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/s/

LEAH S HER
03/06/2017
Hi Guilin,

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than 4 PM (EST) on Monday, March 6, 2017, and follow that with a formal submission to the NDA.

Comments:

1. For patients with a prior history of diabetes or pre-diabetes, describe if antihyperglycemic medication was changed according to the following:
   a. Increase in dose of antihyperglycemic
   b. Addition of a new antihyperglycemic or insulin
   c. Change in therapy from oral medication to insulin

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov
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/s/

LEAH S HER
03/02/2017
Date: February 27, 2017

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Discussion of a clinical PMC and OSI findings

Date and Time of Teleconference: February 9, 2017, approximately 3:00 – 3:30 PM (EST)

FDA Participants:

Jeffrey Summers  Deputy Director of Safety, DOP2
Martha Donoghue  Associate Director (Acting), DOP2
Steven Lemery  Clinical Team Leader, DOP2
Naomi Horiba  Clinical Reviewer, DOP2
Leah Her  Regulatory Health Project Manager, DOP2
Kun He  Statistical Team Leader, DBV
Thomas Ly  Statistical Reviewer, DBV
Lauren Iacono-Connor  OSI Reviewer, GCPAB

Sponsor Participants:

Daniel Bollag  Senior Vice President, Regulatory, Pharmacovigilance and Quality
Douglas Shorten  Director, Program Management
Guilin Huang  Director, Regulatory Affairs
Ronald Knickerbocker  Vice President, Biomedical Data Sciences & Information
Sergio Santillana  Vice President, Clinical Research and Development, Chief Medical Officer
Sean Daly  Vice President, Clinical Operations
Shirish Hirani  Vice President, Drug Development
Shreya Mehta  Senior Associate, Regulatory Affairs
Stephanie Lustgarten  Senior Director, Biostatistics and Statistical Programming
Tim Clackson  President of Research & Development, Chief Scientific Officer
Pat Thomas  Senior Director, Regulatory Affairs (Takeda)

This was a FDA-initiated teleconference to discuss FDA’s newly proposed Postmarketing Commitment (PMC) and the Office of Scientific Integrity (OSI) findings for pending New Drug Application (NDA) 208772 received on August 29, 2016, for the proposed use of brigatinib for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. In advance of this meeting on February 7, 2017, FDA provided an agenda and OSI comments for discussion during the meeting. These correspondences are attached to this memo.

Reference ID: 4061736
Summary of the Tcon:

FDA started by stating for labeling purposes, FDA is proposing a PMC for longer follow-up data for intracranial response rate given that the intracranial response rate and duration of response was insufficiently characterized due to the small number of patients evaluated in Study AP26113-13-201 (ALTA). While FDA acknowledged that ARIAD had previously submitted a courtesy e-copy of a poster containing additional follow-up data to the IND, FDA observed that the ALTA trial allowed for up to 2 years of follow-up. ARIAD acknowledged and stated that ARIAD would provide a proposal for the PMC and the data-cut off dates.

FDA also briefly provided the background for the OSI information request; specifically, that the ORA inspection at the imaging site, uncovered the following:

- various instances of re-reads or changes with vague categorization
- no audit trail
- switch in databases in the middle of the study

Taken together, FDA investigators were unable to verify the IRC-assessed data provided to FDA in the original NDA submission. Based on these findings, FDA stated that a determination could not be made as to whether this issue would impact the overall analysis of efficacy. ARIAD acknowledged FDA’s concerns and stated that they plan to submit responses to the information request, in two parts, Questions 1, 3, 4, 5, 6, 7 and Question 2, as the latter would take more time. FDA acknowledged ARIAD’s plans and stated that ARIAD should submit the responses as soon as possible. FDA alluded to the possibility that the IRC-assessed data (for both the primary endpoint and intracranial response rate) may not be included in the package insert during this review cycle if approved for marketing.

Lastly, FDA reiterated that ARIAD should respond to the information request formally to the NDA, but ARIAD should also respond to ORA regarding the inspection findings. ARIAD expressed understanding and no further discussion occurred.

Attachments:
- Tcon agenda provided on February 7, 2017
- OSI comments and information request provided on February 7, 2017

Reference ID: 4061736
Dear Guilin,

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.” We also refer to our teleconference scheduled for this Thursday, February 9, 2017, at 3:00 PM (EST), to discuss a potential new clinical PMC.

Please see below additional information provided by our clinical team regarding the PMC:

Given the limited amount of data available regarding the intracranial response rate submitted for labeling purposes, we plan to request that ARIAD submit data from longer term follow up to better characterize the duration of intracranial response \[(b)(4)\].

In addition, attached is a memorandum of clinical review comments and information request. We would like to use a part of the scheduled time to discuss the attached new clinical IR.

Kindly confirm receipt of this email and attachment.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information.

Comments:

Provide the following information regarding any changes to entries in the IRC database that occurred after the time of original data entry and prior to database lock and analysis of radiographic efficacy endpoints. Provide this information in a spreadsheet format that can be manipulated and analyzed by our reviewers:

1. The number of data changes that occurred in the IRC database overall and the number of patients whose data was changed.

2. For each data change, provide the following information in a line listing format that is searchable and can be manipulated by FDA reviewers:
   a. Patient identification number
   b. Treatment arm
   c. Category of assessment (Baseline, Post-treatment, etc.)
   d. Study Day of assessment
   e. Type of assessment (CT/MRI, etc.)
   f. Assessment for overall response vs. intracranial response
   g. Nature and category of the data change (etc. change in measurement of target lesion, etc.)
   h. Reason for data change
   i. Date data was originally entered into the database
   j. Date of data change
   k. Previous data entry (prior to data change)
1. New/updated data entry
   m. Identity of the party that initiated data change (sponsor, CRO, radiologist, etc.)
   n. Overall response assessment prior to the data change
   o. Overall response assessment after the data change
   p. Whether the data change resulted in a change in overall assessment of response (yes or no)

3. In November 2015, IRC software was changed. After this change, all previously read and signed off cases were resubmitted to the radiologists for re-evaluation using the new software. Provide available information regarding the reasons for the software change and the re-reads, including whether this was requested by ARIAD. Additionally, provide a listing for each radiograph and time point that was returned for re-evaluation due to this software change that includes the information requested in item 2 above.

4. Any available documentation regarding these data changes, including any correspondence between the CRO and sponsor regarding these data changes.

5. A copy of the original signed IRC charter and all subsequent signed amendments to that charter.

6. A copy of any additional agreements/statements of work/contracts between ARIAD and IRC CRO, \( (b)(4) \) pertaining to Study AP26113-13-201.

7. An assessment regarding whether these data changes resulted in changes to the efficacy analyses for IRC assessment of ORR, DoR, intracranial response rate, and duration of intracranial response.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
02/07/2017
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/s/

LEAH S HER
02/27/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Monday, February 20, 2017, and follow that with a formal submission to the NDA.

Comment:

1. Please clarify whether radiographic images performed between February 29, 2016 and May 31, 2016 contributed to the IRC-assessed analyses of systemic and intracranial responses.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

---------------------------------------------
LEAH S HER
02/16/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information.

Comments:

Provide the following information regarding any changes to entries in the IRC database that occurred after the time of original data entry and prior to database lock and analysis of radiographic efficacy endpoints. Provide this information in a spreadsheet format that can be manipulated and analyzed by our reviewers:

1. The number of data changes that occurred in the IRC database overall and the number of patients whose data was changed.

2. For each data change, provide the following information in a line listing format that is searchable and can be manipulated by FDA reviewers:
   a. Patient identification number
   b. Treatment arm
   c. Category of assessment (Baseline, Post-treatment, etc.)
   d. Study Day of assessment
   e. Type of assessment (CT/MRI, etc.)
   f. Assessment for overall response vs. intracranial response
   g. Nature and category of the data change (etc. change in measurement of target lesion, etc.)
   h. Reason for data change
   i. Date data was originally entered into the database
   j. Date of data change
   k. Previous data entry (prior to data change)
1. New/updated data entry
   m. Identity of the party that initiated data change (sponsor, CRO, radiologist, etc.)
   n. Overall response assessment prior to the data change
   o. Overall response assessment after the data change
   p. Whether the data change resulted in a change in overall assessment of response (yes or no)

3. In November 2015, IRC software was changed. After this change, all previously read and signed off cases were resubmitted to the radiologists for re-evaluation using the new software. Provide available information regarding the reasons for the software change and the re-reads, including whether this was requested by ARIAD. Additionally, provide a listing for each radiograph and time point that was returned for re-evaluation due to this software change that includes the information requested in item 2 above.

4. Any available documentation regarding these data changes, including any correspondence between the CRO and sponsor regarding these data changes.

5. A copy of the original signed IRC charter and all subsequent signed amendments to that charter.

6. A copy of any additional agreements/statements of work/contracts between ARIAD and IRC CRO, \textsuperscript{(b)(4)} pertaining to Study AP26113-13-201.

7. An assessment regarding whether these data changes resulted in changes to the efficacy analyses for IRC assessment of ORR, DoR, intracranial response rate, and duration of intracranial response.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
02/07/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached FDA’s preliminary edits and comments to your revised package insert (PI) labeling submitted on November 21, 2016. Please provide your response via email as soon as possible but no later than 4 PM (EST), Friday, February 10, 2017, and follow that with a formal submission to the NDA.

In the areas of the label that you agree with FDA’s proposed edits, please accept the tracked change to aid in reviewability. For those edits that you do not agree with, provide justification as a comment (cite “From ARIAD” in the comment). For any edits you wish to propose, add via track changes and provide justification as a comment (cite “From ARIAD” in the comment). Lastly, when making edits to the label, please update formatting as necessary.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
01/27/2017
Dear Guilin,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, January 24, 2017.

1. We acknowledge the revised Appearance specification for starting material that you proposed in your 13-DEC-2016 quality information amendment as well as the updated drug substance stability data that you provided. Update the relevant Module 3 sections of the NDA accordingly.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
ARIADE Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We have the following request for information. Please provide your response via email as soon as possible but no later than Monday, January 23, 2017, and follow that with a formal submission to the NDA.

Comments:

General Comment

1. Revise the storage temperature language for consistency, including the order of information and format, between the PI, the container labels and the carton labeling, to state “Store at controlled room temperature 68°F to 77°F (20°C to 25°C); excursion permitted between 59° to 86°F (15°C to 30°C) (See USP).”

Container Labels and Carton Labeling

2. Revise the font color of the proprietary name [highlighted color] or revise the color scheme of the 90 mg strength [highlighted color], so both the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the same color font for the proprietary name and one of the product’s strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

3. The strength expression lacks prominence when compared to the highlighted “Rx only | [highlighted color]” statement on the principal display panel (PDP). Consider using a color block and/or larger font size or bolding to increase the prominence of the strength of the product.
4. Decrease the prominence of the "Rx Only" statement as this information appears more prominent than the strength expression on the PDP. Consider removing the color block from the "Rx Only" statement to make it appear less prominent, and relocate it to another line on the PDP or to another panel.

5. The _______________________________ (9) is not required to appear in the PDP. Consider removing the "(9)" statement from the PDP to reduce crowding of information and to improve readability.

6. Revise the _______________________________ (9) statement on the side panel to read: "Usual Dose: See prescribing information".

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
01/09/2017
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Monday, January 9, 2017, and follow that with a formal submission to the NDA.

Comments:

1. Describe the steps taken to minimize potential bias by Dr. [REDACTED] who holds equity interest in ARIAD for Study AP26113-11-101 as described on Form 3455.

2. Disclose the number of investigators (if any) who are or were also sponsor employees, full or part time.

3. Please provide the total number of investigators (not sites) for each study.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
01/05/2017
NDA 208772

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Alunbrig (brigatinib) Tablets, 30 and 90 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 15, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-6611.

Sincerely,

\{See appended electronic signature page\}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
Meeting Date and Time: December 14, 2016 / 11:00 – 12:00 PM (EST)

Application Number: NDA 208772
Product Name: brigatinib (proposed as ALUNBRIG)
Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Applicant Name: ARIAD Pharmaceuticals Inc.

Meeting Chair: Steven Lemery
Meeting Recorder: Leah Her

FDA ATTENDEES
Richard Pazdur Director, OHOP
Amy McKee Deputy Director (Acting), OHOP
Patricia Keegan Division Director, OHOP/DOP2
Martha Donoghue Associate Director (Acting), OHOP/DOP2
Steven Lemery Clinical Team Lead, OHOP/DOP2
Naomi Horiba Clinical Reviewer, OHOP/DOP2
Monica Hughes Chief, Project Management Staff, OHOP/DOP2
Leah Her Regulatory Health Project Manager, OHOP/DOP2
Alex Putman Nonclinical Reviewer, OHOP/DHOT
Anwar Goheer Nonclinical Reviewer, OHOP/DHOT
Thomas Ly Statistical Reviewer, OB/DBV
Hong Zhao Clinical Pharmacology Team Lead, OTS/OCP/DCPV
Ruby Leong Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Jiang Liu Pharmacometrics Team Lead, OTS/OCP/DPM
Katherine Windsor Product Quality Reviewer, OPQ/OND/DPDAP/NDBI
Joyce Crich Product Quality Team Lead, OPQ/OND/DPDAP/NDBI
Joan Zhao Biopharmaceutics Reviewer, OPQ/OND/DB/BBI
Elizabeth Everhart Senior Drug Risk Analyst, OSE/OMEPRM/DRISK
Carolyn McCloskey Clinical Reviewer, OSE/OPE/DEPII
Rowe Medina Patient Product Information Reviewer, OMP/OMPI/DMPP

APPLICANT ATTENDEES
Daniel Bollag Senior Vice President, Regulatory, Pharmacovigilance and Quality
David Kerstein Senior Medical Director, Clinical Research & Development
Douglas Shorten Director, Program Management
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.

SIGNIFICANT ISSUES

Clinical/Statistics
1. No significant issues have been identified to date.

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.

2. Under 21 CFR 314, Subpart H, complete and submit the results of Protocol AP26113-13-301 as a postmarketing requirement, to verify and describe the clinical benefit of brigatinib.

Discussion: FDA asked ARIAD to submit timelines for completion of Study AP26113-13-301 to the NDA. FDA stated that a correspondence will be issued for agreement on the formal PMR language and timelines on or before January 27, 2017.
Nonclinical

3. No significant issues have been identified to date.

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.

Clinical Pharmacology

4. Evaluate the effect of moderate CYP3A4 inhibitors on brigatinib systemic exposure via physiologically-based pharmacokinetic (PBPK) modeling or conducting a drug-drug interaction (DDI) study as a postmarketing requirement to determine the dose of brigatinib when it is coadministered with moderate CYP3A4 inhibitors.

Discussion: ARIAD stated that PBPK modeling has been initiated and a draft report is anticipated by January 2017. FDA stated that given the timeline of January 2017 or beyond for submission of the draft report, a PMR would likely be requested to address the effect of moderate CYP3A4 inhibitors on brigatinib pharmacokinetics.

5. Evaluate the effect of moderate CYP3A4 inducers on brigatinib systemic exposure via PBPK modeling or conducting a DDI study as a postmarketing commitment to determine the dose of brigatinib when it is coadministered with moderate CYP3A4 inducers.

Discussion: Refer to #4 above. FDA stated that a PMC would likely be requested to address the effect of moderate CYP3A4 inducers on brigatinib pharmacokinetics.

6. Conduct a clinical DDI study as a postmarketing requirement to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of a sensitive CYP3A4 substrate.

Discussion: ARIAD requested clarification on this comment. FDA stated that the reason for requesting this DDI study is based on CYP3A induction by brigatinib in vitro. ARIAD requested FDA to provide a formal information request with FDA’s rationale. FDA agreed and stated that FDA anticipates issuing a communication during the week of December 19, 2016.

7. Complete and submit the renal impairment study as a postmarketing requirement (agreed under the April 15, 2016, pre-NDA meeting).

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.

8. Complete and submit the hepatic impairment study as a postmarketing requirement (agreed under the April 15, 2016, pre-NDA meeting).

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.

Chemistry, Manufacturing and Controls

9. No significant approvability issues have been identified to date.

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.
10. As stated in the CMC IR dated 11/29/2016, review of acceptability of the alternate drug substance supplier, is pending the submission of comparative multipoint dissolution profile data between one clinical/registration batch manufactured using drug substance and a drug product batch manufactured using drug substance.

Discussion: FDA stated that ARIAD’s December 13, 2016 response to FDA’s November 29, 2016 information request is under review. FDA stated that FDA will follow-up with ARIAD, as appropriate, once review of ARIAD’s response is completed.

ARIAD also requested an update on the status of the manufacturing site inspections. FDA stated that these are currently scheduled for January 2017.

PENDING INFORMATION REQUESTS

Clinical
11. On December 8, 2016, FDA provided clinical review comments and information requests which are due by December 15, 2016.

Discussion: FDA acknowledged the receipt of ARIAD’s responses via email and ARIAD stated that a formal submission to the NDA is pending.

Chemistry, Manufacturing and Controls
12. On November 29, 2016 and December 8, 2016, FDA provided CMC review comments and information requests which are due by December 13, 2016.

Discussion: FDA acknowledged the receipt of ARIAD’s responses via email and formally to the NDA for the November 29, 2016, information request, and ARIAD’s responses via email for the December 8, 2016, information request. ARIAD stated that a formal submission to the NDA is pending for the December 8, 2016, information request.

FDA also stated that a request for additional statistical information was issued on December 12, 2016, and a response is due by December 20, 2016.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

13. No unanticipated safety concerns have been identified at this point in the review and it is not expected that a REMS will be needed.

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.

ADVISORY COMMITTEE MEETING

14. There are no plans for an advisory committee meeting at this time; however, Special Government Employees (SGEs) may be consulted during review of this application.

Discussion: ARIAD acknowledged FDA’s comment. No discussion occurred.
LATE-CYCLE MEETING / OTHER PROJECTED MILESTONES

15. Late-Cycle Meeting with Applicant
   a. Monday, March 6, 2017 / 12:00 – 1:00 PM (EST) in person
   b. Background package to the Applicant planned for Wednesday, February 22, 2017

   **Discussion:** FDA stated that the Late-Cycle Meeting has been rescheduled for Friday, February 24, 2016 / 11:00 – 12:00 PM (EST). ARIAD requested clarification on the potential for the Late-Cycle Meeting to occur earlier given the lack of comments in the Post Mid-Cycle Communication. FDA stated that because the review has not been completed and there are other remaining pending discussions, the Late-Cycle meeting date will need to remain as scheduled. FDA stated that FDA will communicate with ARIAD if the date of Late-Cycle Meeting can be moved up.

   ARIAD requested advice on how they could assist in moving up the review and action for this application. FDA stated that ARIAD should continue to respond to FDA requests in a timely manner, or earlier, if possible.

16. Proposed Labeling and Potential PMRs/PMCs to Applicant
   a. Friday, January 27, 2017

   **Discussion:** ARIAD acknowledged FDA’s comment. No discussion occurred.
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/s/

LEAH S HER
01/03/2017
Application: NDA 208772
Product: Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date: August 29, 2016
Received Date: August 29, 2016
Applicant: ARIAD Pharmaceuticals Inc.
Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees: Patricia Keegan, Martha Donoghue, Steven Lemery, Naomi Horiba, Jennie Chang, Abhi Nair, Damiete Smit, Monica Hughes, Leah Her, Kun He, Thomas Ly, Hong Zhao, Ruby Leong, Thomas Gwiese, Jiang Liu, Hongshan Li, Whitney Helms, Anwar Goheer, Joyce Crich, Steven Kinsley, Katherine Windsor, Joan Zhao, Latonia Ford, Janine Stewart, Peter Waldron, Afrouz Nayernama, Carolyn McCloskey, Elizabeth Everhart, Jade Chen, Jonathan Goldsmith, Nazia Fatima, Rowe Medina, Ruth Moore, Thuy Thanh Nguyen

Discussion During the Meeting:

1. Slides were presented by the following disciplines (in order):
   - Regulatory Introduction – Leah Her
   - CMC – Joyce Crich
   - Nonclinical – Anwar Goheer
   - Clinical Pharmacology/Pharmacometrics – Ruby Leong, Hongshan Li
   - Clinical/Statistical – Naomi Horiba, Thomas Ly

2. Key Issues:
   - CMC:
     Discussion: Biopharmaceutics stated that this original NDA lacked the appropriate bridging data for the proposed alternate drug substance source. Biopharmaceutics stated that an IR will be issued to request comparative multipoint dissolution profile data. If the provided information is insufficient, then the alternate site may have to be withdrawn from this original NDA and submitted, with adequate supporting data, under a supplement.

   An update on the status of manufacturing site inspections were provided. Facilities informed the Review Team that two of the three planned sites are scheduled for January 2017. The third site is not intended to be inspected under this NDA as the last three surveillance inspections (last one July 2016) resulted in NAI findings.

   - Nonclinical:
     Discussion: The Nonclinical Team stated that no issues have been identified to date, and is not expecting to require any postmarketing studies at this time.
• Clinical Pharmacology/Pharmacometrics:

Discussion: The Clinical Pharmacology/Pharmacometrics Team stated that potential PMRs/PMCs pertaining to DDI studies will be discussed during the Post Mid-Cycle Communication meeting. Additionally, the Applicant will be reminded regarding the previously agreed postmarketing renal and hepatic impairment studies.

• Clinical/Statistical:

Discussion: The Clinical Team indicated that an IR will be issued for additional information regarding Study 201, and will request an update on the duration of response observed in Study 201 during the Post Mid-Cycle Communication meeting. Additionally, the Clinical Team stated that the required PMR for a confirmatory trial will be reiterated.

A brief update on the status of clinical site inspections was discussed. All planned clinical site inspections were completed. The inspection of the Applicant is currently being planned.

3. Advisory Committee:

Discussion: The Team determined at this point in time that an ODAC will not be held for this application. Special Government Employees (SGEs) may be consulted individually.

4. Discussion on potential PMC/PMR or REMS:

Discussion: The Team determined at this point in time that a REMS will not be needed. Please refer to section 2 regarding discipline-specific PMRs and PMCs.
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/s/

LEAH S HER
01/03/2017
From: Steven Kinsley
To: guilin.huang@ariad.com
Cc: Leah Her
Subject: NDA 208772 CMC Information Request 1-3-17

Dear Guilin,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, Jan. 6, 2017.

1. Two of ten results from Lot 140132 were reported outside of the range %. You stated they were caused by an analytical error. Provide the duplicate test results for samples -4 and -5.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Thursday, January 5, 2017, and follow that with a formal submission to the NDA.

Comments:

1. Provide an analysis of brigatinib’s effects on heart rate including data collected from vital signs in both Studies 101 and 201.

2. Reference is made to Table 14.3.7.4 and 14.3.7.5 in the CSR for ALTA (e.g. in Table 12-15) but the tables are unable to be located. Please inform as to the location of the tables or provide the tables.

3. Provide the recommended approach for re-initiating brigatinib at 90 mg after dose interruption for toxicity or unintentional missed dosing (e.g. after xx day(s) of interruption, restart at 90 mg daily for 7 days prior to escalating to 180 mg daily).

4. Provide an assessment of response and summary of toxicity for the two patients that were intolerant to crizotinib from 101.

5. Please report if anyone who crossed over from ARM A to ARM B for progression of disease had a response.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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-/s-/  

LEAH S HER  
12/22/2016
Date: December 22, 2016

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

NDA Review Timeline and Late-cycle Meeting Date

Date and Time of Teleconference: December 12, 2016, approximately 9:40 – 9:45 AM (EST)

FDA Participant:
Leah Her Regulatory Health Project Manager, DOP2

Sponsor Participant:
Guilin Huang Associate Director, Regulatory Affairs

This was a FDA-initiated teleconference to follow-up on a voicemail left by the ARIAD Contact, for the pending New Drug Application (NDA) 208772 received on August 29, 2016, for the proposed use of brigatinib for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Background:

On December 9, 2016, FDA issued the Post Mid-cycle Communication Meeting Agenda for NDA 208772. Upon receipt, the ARIAD Contact requested via an electronic mail (email) communication to discuss the potential to move up the date of the Late-cycle Meeting (scheduled for March 6, 2017).

Summary of the Tcon:

The ARIAD Contact requested to push up the currently scheduled Late-cycle Meeting date in March to a much earlier timeframe around January, based on 1) ARIAD availability, and 2) ARIAD’s assumption that the application review is uneventful based on their review of the Post Mid-cycle Communication Agenda. The ARIAD Contact also inquired on the NDA review timelines post-Late-cycle Meeting; specifically, regarding whether the Action could take place earlier.

The FDA RPM stated that the Late-cycle Meeting date is based on the PDUFA V Program timeline, for which the meeting date is around Month 6 of the review cycle for applications under Priority Review. The FDA RPM stated that the Post Mid-cycle Communication is a snapshot of FDA’s thinking and concerns regarding the application at a specific point in time; and therefore, it is premature in the review cycle to make an assumption that review is uneventful. The FDA RPM stated that based on the reasons outlined above, the Late-cycle
meeting date could not be rescheduled to occur at a much earlier timeframe (around January); however, the Late-cycle meeting could potentially be rescheduled to a date approximately 1 week earlier than currently scheduled based on the FDA Review Team’s availability. The FDA RPM stated that the ARIAD Contact will be provided a confirmation of the revised meeting date once formally rescheduled. The ARIAD Contact expressed understanding.

The FDA RPM also stated that the FDA RPM could not speak to an earlier action date that is different from the currently scheduled PDUFA Action Date of April 29, 2017. The ARIAD Contact expressed understanding.
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/s/

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LEAH S HER
12/22/2016
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  

Memorandum

**Date:** December 22, 2016  
**From:** Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2  
**Subject:** NDA 208772 – ARIAD Pharmaceuticals, Inc.  
Proposed Post Marketing Requirement

ARIAID Pharmaceuticals, Inc.  
Attention: Guilin Huang, M.B.A., R.A.C.  
Associate Director, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

In order to confirm clinical benefit as stipulated/required under 21 CFR 314.510, you should plan to conduct the following Post Marketing Requirement (PMR). Please note that additional PMR and PMC proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposal. We remind you to use due diligence in proposing timelines for completion of these trials. Please provide a response by 4 PM (EST) on Friday, January 6, 2017, or sooner if possible.

**POST MARKETING REQUIREMENT**

**Clinical**

1. Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of brigatinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

PMR/PMC Schedule

Milestones:

- Study/Trial Completion: MM/DD/YYYY  
- Final Report Submission: MM/DD/YYYY

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
12/22/2016
**Team Meeting Summary**  
**November 9, 2016**

**Application:** NDA 208772  
**Product:** Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg  
**Submission Date:** August 29, 2016  
**Received Date:** August 29, 2016  
**Applicant:** ARIAD Pharmaceuticals Inc.  
**Proposed Indication:** ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

**Attendees:** Martha Donoghue, Naomi Horiba, Leah Her, Whitney Helms, Anwar Goheer, Emily Wearne, Thomas Ly, Steven Kinsley, Katherine Windsor, Hong Zhao, Ruby Leong, Jiang Liu, Hongshan Li, Lauren Iacono-Connor, Joan Zhao, Elizabeth Everhart, Thuy Nguyen, Carolyn McCloskey, Latonia Ford, Amy McKee, Rowe Medina, Nazia Fatima

* The Review Team was reminded that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

**AGENDA**

1. **Review Status**

   **Discussion:** Applicant’s NDA submission contents and requests previously discussed. No discussion occurred.

2. **Application Milestone**

   **Discussion:** The timelines based on a priority review were provided to the Team. No discussion occurred.

3. **Upcoming Internal Team Meetings**

   **Discussion:** The Team was reminded that the Mid Cycle Meeting was the next milestone, and scheduled for Tuesday, 11/29/16. The Team was reminded that slides were due to CDTL 1 week prior to the Mid Cycle Meeting.

   The Team was provided with the revised labeling meeting schedule. The revised label is due from ARIAD on or before 11/18/16. The Team was also provided with the monthly team meeting schedule. No discussion occurred.

4. **Team Updates**

   **Discussion:** Clinical provided a brief update on the efforts to identify and obtain Special Government Employees (SGE). Four potential SGEs/existing RGEs contacted were not able to move forward due to various reasons, 2 are currently under consideration pending initial screening or conflict of interest clearance, and 2 have not yet responded. RPM/Clinical Reviewer will try to call the latter two potential SGEs.

   CMC provided a brief update on the status of CMC review, including outstanding and new information requests (see agenda item 5 below). CMC also provided an update on the facility inspection status.

Reference ID: 4031858
Clinical Pharmacology provided a brief update on the population PK dataset issue and requested that a tcon is scheduled with ARIAD to discuss the issue.

For all other disciplines, reviews are on track and no issues were discussed at this point in time.

5. Information Request Status

Discussion: The Team discussed that there were few outstanding information requests (IR) at this point in time as follow:

- **Clinical Pharmacology**  
  - IR issued 11/7/16 regarding PPK dataset/model; due 11/8/16 & 11/14/16
- **Chemistry, Manufacturing and Controls**  
  - IR issued 10/28/16 in Filing Letter regarding labels; due 11/18/16
  - IR issued 11/4/16 regarding HPLC specification; due 11/18/16
- **Labeling**  
  - IR issued 10/28/16 in Filing Letter regarding PI; due 11/18/16

CMC anticipated sending out a new IR for process-related issues.

6. Consult Status

Discussion: During this period, the QT-IRT consult review was completed on 11/6/16. All other consults are on track and no additional discussion occurred.

7. Shared Review Pilot

Discussion: This application will be under the shared review pilot. This pilot is intended for core disciplines; specifically, clinical, nonclinical, clinical pharmacology. The Team was given a brief overview of the pilot. The applicable disciplines were reminded that:

- only their applicable sections should be modified
- contact the administrator (Tamy Kim) to obtain access to the shared review
- final signatures will be conducted in DARRTS rather than in sharepoint
- section 10 labeling recommendations will be completed by the applicable disciplines rather than the ADL

The location of shared review, general instructions, and the brigatinib shared review procedure were provided but due to lack of time, the procedure was not discussed in detail.

8. MISC Items or Issues

Discussion: None.

9. Review Action Items and Decisions

Discussion: RPM to set up a tentative tcon with Applicant to discuss population PK dataset issue.
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/s/

LEAH S HER
12/21/2016
Application: NDA 208772
Product: Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date: August 29, 2016
Received Date: August 29, 2016
Applicant: ARIAD Pharmaceuticals Inc.
Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees: Martha Donoghue, Steven Lemery, Naomi Horiba, Leah Her, Thomas Ly, Hong Zhao, Ruby Leong, Hongshan Li, Anwar Goheer, Joyce Crich

* The Review Team was reminded that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

AGENDA

1. Review Status

Discussion: Applicant’s NDA submission contents and requests previously discussed. No discussion occurred.

2. Application Milestone

Discussion: The Team was reminded of the timelines associated with review of the post-mid cycle communication agenda and the revised label. No discussion occurred.

3. Upcoming Internal Team Meetings

Discussion: The Team was reminded that the labeling meetings are scheduled starting mid-December. No discussion occurred.

4. Team Updates

Discussion: None.

5. Information Request Status

Discussion: None.

6. Consult Status

Discussion: None.

Reference ID: 4031873
7. Shared Review Pilot

Discussion: The main purpose of this meeting was to discuss the specific shared review procedure for this application. The Team reviewed the procedure and timelines associated with the shared review.

8. MISC Items or Issues

Discussion: None.

9. Review Action Items and Decisions

Discussion: None.
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/s/

LEAH S HER
12/21/2016
ARRID Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We propose the following Post Marketing Commitments (PMCs) and Post Marketing Requirements (PMRs). Please note that additional PMR and PMC proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposal. We remind you to use due diligence in proposing timelines for completion of these trials. Please provide your response via email as soon as possible but no later than Friday, January 6, 2017.

POST MARKETING REQUIREMENTS

1. Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.” Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for excessive drug toxicity may be acceptable.

PMR/PMC Schedule
Milestones:

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2. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

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Milestones:

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3. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with 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.”

PMR/PMC Schedule
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**POST MARKETING COMMITMENTS**

4. Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.” Alternatively, use of a physiologically-based pharmacokinetic modeling approach to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations may be acceptable.

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5. Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of a sensitive CYP3A4 substrate to address the magnitude of decreased exposure of the substrate. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

PMR/PMC Schedule
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Rationale for this potential PMC: According to the 2012 FDA Draft Drug Interaction Studies Guidance for Industry (Figure 2), if an investigational drug is an interacting drug of an enzyme, conduct in vivo studies with most sensitive/specific substrate(s). Brigatinib may induce CYP3A at clinically relevant concentrations based on human hepatocytes and PXR activation study in vitro; therefore, an in vivo evaluation should be conducted using a sensitive CYP3A substrate (e.g., midazolam).

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

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LEAH S HER
12/20/2016
From: Steven Kinsley  
To: guilin.huang@ariad.com  
Cc: Leah Her  
Subject: NDA 208772 CMC Information Request 12-16-16  
Date: December 16, 2016  

Dear Guilin,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, January 06, 2017.

1. Amend section 3.2.P.5.4 to include the drug product batch data for the 30 mg batch 011700, manufactured at Penn using the [redacted] drug substance batch 608030003 and the 90 mg batch 011701, manufactured at Penn with the [redacted] drug substance batch 608030002.

2. Based on our analysis on your provided dissolution data, an acceptance criterion of Q = [redacted] % at 20 minutes is deemed appropriate for the proposed Brigatinib Tablets. Be aware that setting of the dissolution acceptance criterion is based on S2 testing (n=12); therefore, Stage 2 testing and occasional Stage 3 testing maybe needed.

Submit a revised drug product Specifications table accordingly and start collecting stability dissolution data at 20 minutes at your next stability time point and thereafter.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations  
U.S. Food and Drug Administration  
Tel: 240-402-2773  
Steven.Kinsley@fda.hhs.gov
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We also refer to our November 23, 2016, request for statistical information and your December 7, 2016, response.

The Statistical Reviewer has the following additional request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Tuesday, December 20, 2016, and follow that with a formal submission to the NDA.

Comments:

1. Explain the discrepancy in datasets generated by the ADLS.sas and ADEFF.sas programs (submitted 12/7/16) and the ADLS and ADEFF ADaM datasets submitted on 8/29/16.

   - The ADLS dataset generated by the ADLS.sas program provided contains N=21,592 observations but the ADLS dataset submitted on 8/29/16 contains N=19,061 observations.

   - Clarify why the number of confirmed responses (CONFORFL variable) differs between the ADEFF dataset generated by the ADEFF.sas program provided (submitted on 12/7/16) and the ADEFF dataset submitted on 8/29/16.

      o ADEFF dataset generated by ADEFF.sas (submitted on 12/7/16):

      | Confirmed ORR |    |    |    |
      | CONFORFL     | Frequency | Percent | Cumulative Frequency | Cumulative Percent |
      | N            | 335       | 56.11   | 335                  | 56.11              |

Reference ID: 4026281
Confirmed ORR

<table>
<thead>
<tr>
<th>CONFORFL</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>262</td>
<td>43.89</td>
<td>597</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Frequency Missing = 69

- ADEFF dataset submitted on 8/29/16:

Confirmed ORR

<table>
<thead>
<tr>
<th>CONFORFL</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>339</td>
<td>56.78</td>
<td>339</td>
<td>56.78</td>
</tr>
<tr>
<td>Y</td>
<td>258</td>
<td>43.22</td>
<td>597</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Frequency Missing = 69

2. Please clarify how the TM2NXCYC variable was used in the definition of confirmed ORR. Furthermore, clarify how subjects who used non-protocol therapy were treated in the calculation of confirmed ORR and other study endpoints.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
12/12/2016
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

Please find attached agenda for the Post Mid-Cycle Communication Meeting scheduled as a teleconference for Wednesday, December 14, 2016 between 11:00 – 12:00 PM (EST). We are confirming the following teleconference number:

Teleconference No.: 1-855-244-8681
Conference ID: [Redacted]

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
- Post Mid-Cycle Communication Meeting Agenda
POST MID-CYCLE COMMUNICATION MEETING AGENDA

Meeting Date and Time: December 14, 2016 / 11:00 – 12:00 PM (EST)
Location: NA; teleconference

Application Number: NDA 208772
Applicant Name: ARIAD Pharmaceuticals Inc.
Product Name: brigatinib (proposed as ALUNBRIG)
Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

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.

SIGNIFICANT ISSUES

Clinical/Statistics
1. No significant issues have been identified to date.
2. Under 21 CFR 314, Subpart H, complete and submit the results of Protocol AP26113-13-301 as a postmarketing requirement, to verify and describe the clinical benefit of brigatinib.

Nonclinical
3. No significant issues have been identified to date.

Clinical Pharmacology
4. Evaluate the effect of moderate CYP3A4 inhibitors on brigatinib systemic exposure via physiologically-based pharmacokinetic (PBPK) modeling or conducting a drug-drug interaction (DDI) study as a postmarketing requirement to determine the dose of brigatinib when it is coadministered with moderate CYP3A4 inhibitors.
5. Evaluate the effect of moderate CYP3A4 inducers on brigatinib systemic exposure via PBPK modeling or conducting a DDI study as a postmarketing commitment to determine the dose of brigatinib when it is coadministered with moderate CYP3A4 inducers.
6. Conduct a clinical DDI study as a postmarketing requirement to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of a sensitive CYP3A4 substrate.

7. Complete and submit the renal impairment study as a postmarketing requirement (agreed under the April 15, 2016, pre-NDA meeting).

8. Complete and submit the hepatic impairment study as a postmarketing requirement (agreed under the April 15, 2016, pre-NDA meeting).

Chemistry, Manufacturing and Controls
9. No significant approvability issues have been identified to date.

10. As stated in the CMC IR dated 11/29/2016, review of acceptability of the alternate drug substance supplier, is pending the submission of comparative multipoint dissolution profile data between one clinical/registration batch manufactured using drug substance and a drug product batch manufactured using substance.

PENDING INFORMATION REQUESTS

Clinical
11. On December 8, 2016, FDA provided clinical review comments and information requests which are due by December 15, 2016.

Chemistry, Manufacturing and Controls
12. On November 29, 2016 and December 8, 2016, FDA provided CMC review comments and information requests which are due by December 13, 2016.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

13. No unanticipated safety concerns have been identified at this point in the review and it is not expected that a REMS will be needed.

ADVISORY COMMITTEE MEETING

14. There are no plans for an advisory committee meeting at this time; however, Special Government Employees (SGEs) may be consulted during review of this application.

LATE-CYCLE MEETING / OTHER PROJECTED MILESTONES

15. Late-Cycle Meeting with Applicant
   a. Monday, March 6, 2017 / 12:00 – 1:00 PM (EST) in person
   b. Background package to the Applicant planned for Wednesday, February 22, 2017

16. Proposed Labeling and Potential PMRs/PMCs to Applicant
   a. Friday, January 27, 2017
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/s/

LEAH S HER
12/09/2016
Date: December 8, 2016

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Labeling Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We have the following request for information. Please provide your response via email as soon as possible but no later than Tuesday, December 13, 2016 and follow that with a formal submission to the NDA.

Comments:

1. The language in Section 16 of the proposed Prescribing Information indicates Alunbrig tablets should [REDACTED] With the proposed dosing schedule and possible dose modifications for adverse reactions, the currently proposed package configurations (21, [REDACTED] and 180-counts for 30 mg; 30-count for 90 mg) do not meet the quantity needed for dispensing associated with starting dose and dose modifications given the usual clinical practice is to prescribe 1- or 3-month supply. Propose a packaging strategy that allows for pharmacy dispensing of Alunbrig quantities not captured by the currently proposed packaging configurations.

   Such data may include assay data associated with Figure 12 found in section 3.2.P.2.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
12/08/2016
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Thursday, December 15, 2016, and follow that with a formal submission to the NDA.

Comments:

1. Please provide an analysis of response rate for patients whose best response was disease progression during crizotinib treatment.

2. Explain how patients with a best response of “unknown” were randomized as randomization was stratified by response to crizotinib.

3. Please provide information on those patients who did not progress on crizotinib prior to being randomized. Include the number of patients considered intolerant and the definition of intolerance.

4. Provide updated datasets supporting the analyses provided for duration of response.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
12/08/2016
Dear Guilin,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, December 13, 2016.

**Drug Substance**

1. We note that a product [redacted]. Provide justification (e.g., a brief summary of studies or data) for your assertion that [redacted] will not impact product quality, particularly the impurity profile.

2. Justify (e.g., provide results from spike/purge studies) each of the specified impurity limits in the proposed [redacted] specification.

3. We note the range in color of the proposed appearance specification and provided batch data for [redacted]. Briefly discuss the origin of this color variation and justify the broad range of accepted appearances for [redacted] starting material.

4. We recommend you replace the heavy metals test (USP <231>) with elemental impurities testing (USP <232>/<233>) in the drug substance specification.

5. Provide any updated stability data for the registration batches (608030001, 608030002, 608030003) and for Lot 15-420-012 packaged in the optimized commercial configuration.

**Drug Product**

6. Section 16 of the package insert indicates that the 30 mg tablets will be available in 21-count, [redacted] and 180-count presentations in bottles. Section 3.2.P.7 in the NDA indicates that only the 21-count and 180-count presentations will be marketed. Revise either the package insert or section 3.2.P.7 to accurately represent the proposed marketed presentations. If the [redacted] presentation will be marketed, confirm that the container closure configuration is the same 33/400 mm HDPE bottle [redacted] as used for all other presentations of the 30 mg tablets.

7. Section 1.14.1.1 of the NDA includes a bottle and carton label for a 7-count presentation of the 90 mg tablets, but this presentation is not listed in the package insert as a presentation to be marketed. Clarify the intended purpose of this presentation in the NDA or remove the label.
8. We could not locate batch information for (b)(4) used in the comparative dissolution study to support the drug substance site and the registration lots were formulated with drug substance from (b)(4) only. To support the drug substance site at (b)(4), provide comparative multipoint dissolution profile data between one clinical/registration batch manufactured using (b)(4) drug substance and a drug product batch manufactured using (b)(4) drug substance, using the proposed dissolution method for both 30 and 90 mg strengths.

Compare the dissolution profiles between the registration/clinical drug product batches and one batch made with (b)(4) using the similarity factor (f2) or some other appropriate statistical approach. Provide the date of manufacturing for each drug product batch. If the clinical and/or registration batches are older than the proposed shelf life, supportive historical dissolution data may be used for the comparison.

9. While a summary of the results of experiments conducted to validate the proposed method is in the NDA, a full validation report for the dissolution method appears to be missing. Provide the dissolution method validation report PR166-044A and method transfer protocol (b)(4) or refer to the location of the report in the Application.

In addition, based on the provided dissolution data, an acceptance criterion of Q(b)(4) % at 20 minutes is recommended for your proposed Brigatinib Tablets. Be aware that setting of the dissolution acceptance criterion is based on S2 testing (n=12); therefore, Stage 2 testing and occasional Stage 3 testing maybe needed.

Submit a revised drug product Specifications table accordingly and start collecting stability dissolution data at 20 minutes at your next stability time point and thereafter.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 23, 2016
From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2
Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Statistics Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Statistical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Wednesday, December 7, 2016, and follow that with a formal submission to the NDA.

Comment:

1. Provide executable SAS program(s) with adequate documentation to allow FDA to duplicate the analysis datasets from raw (SDTM) datasets for ORR, PFS, and OS analyses for both investigator and IRC assessments. Also, provide SAS programs and documentation to duplicate the analysis datasets for the Intracranial ORR analysis.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 4018092
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/s/

LEAH S HER
11/23/2016
Dear Guilin,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, November 22, 2016.

1. We acknowledge that you have provided justification for the small batch size than usual. Acknowledge that you will submit the scale up information with appropriate submission category after approval, if needed.

2. We acknowledge that the test will be conducted for product manufactured at site. We also acknowledge that the sampling approach will be conducted for product manufactured at Penn. Provide the following information:
   a. The test results for primary stability batches (140132B, 140133B and 140134B) manufactured at site.
   b. You are recommended to perform sampling and submit the sampling plan for review. Evaluate your proposed acceptance criteria and statistical properties (for example, confidence, coverage, ability for a future sample to meet the USP and provide justification in your response. We recommend that your protocol also evaluate between and within location variances for your stratified sampling plan. Refer to the level II Q/A, published on

3. Provide the in-process control (IPC) results for all primary stability batches manufactured at Penn.

4. You did not include the microbiology control in the drug product release specifications in Section 3.2.P.5, but provided the results in Section 3.2.P.8. Clarify whether you plan to include the microbiology test in the future stability study.
If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 7, 2016
From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2
Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Clinical Pharmacology Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Pharmacology Reviewer has the following request for information. Please provide your response via email by the requested dates below and follow that with a formal submission to the NDA.

Comments:

1. The dataset submitted on 11/03/2016 or 10/21/2016 does not match the dataset used in Model run3001.ctl (see information below). Neither dataset worked with NONMEM code run3001.ctl. Please submit the right dataset (nm_pk_26Oct2016.csv) as soon as possible but no later than by 4 PM (EST) on Tuesday, November 8, 2016.

Information for Item 1:
ARIAD's PPK dataset used in Model run3001.ctl (nm_pk_26Oct2016.csv)
according to output file run3001.ctl.lst
TOT. NO. OF OBS RECS: 5741
TOT. NO. OF INDIVIDUALS: 443

PPK dataset submitted on 11/03/2016 (npkoct 16.xpt)
TOT. NO. OF OBS RECS: 5427
TOT. NO. OF INDIVIDUALS: 443

PPK dataset submitted on 10/21/2016 (npkoct 16.xpt)
TOT. NO. OF OBS RECS: 5337
TOT. NO. OF INDIVIDUALS: 431

2. According to the original submission, there is a systemic bias in CWRES-Time plot that indicated an increasing population CL/F with time. If run3001.ctl resulted in similar bias, please revise the PPK model to reduce the bias of CWRES-Time plot, and submit the new model as soon as possible but no later than by 4 PM (EST) on Monday, November 14, 2016.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 4009925
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LEAH S HER
11/07/2016
Dear Guilin,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, November 18, 2016.

1. The acceptance criteria for identification by HPLC is defined in section 3.2.P.5.2.3 as “A match is successful if the retention time of the brigatinib peak in the sample preparation corresponds to the retention time for brigatinib in the reference standard within %.” Section 3.2.P.5.1 defines the acceptance criteria of identification by HPLC to be correspondence of retention times within %. Revise the specification for identification by HPLC to agreement of the standard and sample retention times to be within %.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
NDA 208772

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Alunbrig (brigatinib) Tablets, 30 and 90 mg.

We also refer to your amendments dated September 2, 15, 16, 27 and 30, 2016 and October 7 and 21, 2016.

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 April 29, 2017. 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).

In addition, the planned date for our internal mid-cycle review meeting is November 29, 2016. 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. Please 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.

We request that you submit the following information no later than November 18, 2016:

Chemistry, Manufacturing and Controls

1. Resubmit revised primary and secondary labels that include linear bar codes as required by 21 CFR 201.25 and remove QR codes that are currently in the space for bar codes.
2. The primary container labels do not include the lot number and expiration date. Resubmit primary container labels that demonstrate the location and size of the lot number and expiration date.

Clinical Pharmacology

3. For Study 201, there are 13 subjects with brigatinib concentrations available based on "adpc.xpt" and "pc.xpt" datasets, but those subjects were excluded from NONMEM dataset "nm_pk_6aug2016.xpt" without explanation in the population PK report. Those 13 subjects are: 1001, 44001, 204001, 208007, 607006, 612005, 615001, 615006, 627001, 627003, 763003, 918012, and 995001. Please justify the exclusion of those subjects in the population PK analysis. Otherwise, update your population PK analysis dataset with those subjects included.

4. For Study 201, there are BID doses for subjects before Cycle 2 based on "adexd.xpt", but those BID doses are not reflected in the dosing records of "nm_pk_6aug2016.xpt". Please correct the dosing records of the population PK dataset so that the BID doses are correctly reflected.

5. For Subject 609008 of Study 201, WT is blank in the population PK dataset. Therefore, the analysis using NONMEM had set the subject’s body weight to 0 in estimating this subject’s individual V1 and CL. Please update the dataset by the subject’s actual body weight or update the NONMEM code by a reasonable imputation.

6. Double check whether other mistakes exist in the population PK analysis for Study 201. Afterwards, check whether all similar mistakes exist in the other studies of the population PK dataset. Submit the updated dataset and population PK analysis within one week.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
During our preliminary review of your submitted labeling, we have identified several labeling issues. These issues are described using the track changes and “comment” function within the text of your labeling, and are included as an attachment to this letter. Please review all of the issues identified and revise your labeling accordingly.

We request that you resubmit revised labeling (in Microsoft Word format, both clean and redlined (track changes shown) versions) that addresses these issues by November 18, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

Reference ID: 4005487
Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

MARTHA B DONOGHUE on behalf of PATRICIA KEEGAN
10/28/2016
Date: October 19, 2016

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Clinical Pharmacology Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Pharmacology Reviewer has the following request for information regarding the population PK analysis dataset for brigatinib. Please provide your response via email as soon as possible but no later than by 4 PM (EST) on Thursday, October 27, 2016, and follow that with a formal submission to the NDA.

Comments:

1. For Study 201, there are 13 subjects with brigatinib concentrations available based on "adpc.xpt" and "pc.xpt" datasets, but those subjects were excluded from NONMEM dataset "nm_pk_6aug2016.xpt" without explanation in the population PK report. Those 13 subjects are: 1001, 44001, 204001, 208007, 607006, 612005, 615001, 615006, 627001, 627003, 763003, 918012, and 995001. Please justify the exclusion of those subjects in the population PK analysis. Otherwise, update your population PK analysis dataset with those subjects included.

2. For Study 201, there are BID doses for subjects before Cycle 2 based on "adexd.xpt", but those BID doses are not reflected in the dosing records of "nm_pk_6aug2016.xpt". Please correct the dosing records of the population PK dataset so that the BID doses are correctly reflected.

3. For Subject 609008 of Study 201, WT is blank in the population PK dataset. Therefore, the analysis using NONMEM had set the subject’s body weight to 0 in estimating this subject’s individual V1 and CL. Please update the dataset by the subject’s actual body weight or update the NONMEM code by a reasonable imputation.

Double check whether other mistakes exist in the population PK analysis for Study 201. Afterwards, check whether all similar mistakes exist in the other studies of the population PK dataset. Submit the updated dataset and population PK analysis within one week.

Reference ID: 4001491
If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
10/19/2016
Date: October 14, 2016

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

Statistics Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Statistical Reviewer has the following request for information. Please provide your response to via email as soon as possible but no later than by 4 PM (EST) on Wednesday, October 19, 2016, and follow that with a formal submission to the NDA.

Comment:

1. Provide the SAS codes used to generate the tables and figures in the CSR for Trial AP26113-13-201.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.

Reference ID: 3999420
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/s/

LEAH S HER
10/14/2016
Memorandum

Date: October 6, 2016
From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2
Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Pharmacology Reviewer has the following request for information. Please provide your response via email as soon as possible but no later than by 4 PM (EST) on Thursday, October 20, 2016, and follow that with a formal submission to the NDA.

Comments:

Please provide a response to the following information requests. Alternatively, if you have already submitted this information, please provide the specific location in the file where it can be located.

1. Compare the first-7-day safety profiles (including early onset pulmonary events) between patients on brigatinib 90 mg QD and patients on 180 mg QD.

2. With regards to the effect of organ dysfunction on brigatinib exposure:
   a. Update the population pharmacokinetic dataset with the classification of renal and hepatic function of patients:
      - Normal renal function, mild, moderate, or severe renal impairment based on CLcr and/or eGFR.
      - Normal hepatic function, mild, moderate, or severe hepatic impairment based on NCI criteria.
   b. Include available renal and hepatic function parameters such as SCr, CLcr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, total bilirubin, etc. for each patient.
c. Use boxplot to compare the population PK derived exposure (e.g., AUC, CL/F) between patients with normal renal function and patients with mild, moderate, or severe (if any) renal impairment with the sample size of each category listed below the box.

d. Use boxplot to compare the population PK derived exposure (e.g., AUC, CL/F) between patients with normal hepatic function and patients with mild, moderate, or severe (if any) hepatic impairment (based on NCI criteria), with the sample size of each category listed below the box.

3. With regards to the dose recommendation for concomitant use of moderate CYP3A4 inducers:

a. Provide a comparison of brigatinib exposure between patients with and without concomitant use of moderate CYP3A4 inducers (including dexamethasone) using data from Studies 101 and 201. Identify the patients with concomitant use of moderate CYP3A4 inducers and include information on the dose and duration of the moderate CYP3A4 inducer and time of administration with respect to brigatinib.

b. Provide justification for your proposed labeling recommendation to avoid concomitant use of moderate CYP3A4 inducers supported by PBPK modeling and simulation.

c. In the absence of PBPK analyses, propose a postmarketing study to assess the effect of moderate CYP3A4 inducers on brigatinib systemic exposure.

4. With regards to the dose recommendation for concomitant use of moderate CYP3A4 inhibitors:

a. Provide a labeling recommendation for concomitant use of moderate CYP3A4 inhibitors supported by PBPK modeling and simulation.

b. In the absence of PBPK analyses, propose a postmarketing study to assess the effect of moderate CYP3A4 inhibitors on brigatinib systemic exposure.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

----------------------------------------
LEAH S HER
10/06/2016
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for
step-wise submission of sections of a marketing application under 506 of the Federal Food,
Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The OSI Reviewer has the following request for information. Please provide your response to
via email by 4 PM (EST) on Thursday, October 20, 2016 or sooner if possible, and follow
that with a formal submission to the NDA.

Comment:

1. As Protocol AP26113-13-201 was modified on numerous occasions which includes both
revisions and addendums to the revisions, provide a detailed summary of changes
between each version of the protocol that was used and implemented for the conduct of
the study. If this summary document has already been submitted to the NDA, please
provide the specific location in the file where it can be located.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
10/06/2016
Dear Ms. Huang,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, October 6, 2016.

1. Submit a revised 356h with the site listed below included as a DS intermediate manufacturer:

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
Application: NDA 208772
Product: Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date: August 29, 2016
Received Date: August 29, 2016
Sponsor: ARIAD Pharmaceuticals Inc.

Proposed Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees: Martha Donoghue, Steven Lemery, Naomi Horiba, Leah Her, Whitney Helms, Anwar Goheer, Kun He, Thomas Ly, Katherine Windsor, Olen Stephens, Steven Kinsley, Rakhi Shah, Hongshan Li, Joan Zhao, Lauren Iacono-Connor, Naomi Redd, Afrouz Nayernama, Janine Stewart, Elizabeth Everhart, Ruth Moore, Hong Zhao, Rosane Charlab Orbach, Anuradha Ramamoorthy, Jennie Chang, Rowe Medina, Nazia Fatima

* The Review Team was reminded that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Brief List of Regulatory Interactions

Discussion: The Team briefly discussed the key regulatory background pertaining to brigatinib development program.

AGENDA

1. Review Status

Discussion: The Team briefly discussed the Applicant’s NDA submission contents and requests.

2. Application Milestone:

Discussion: The Team discussed the review timelines. The Team confirmed that the application will be under a priority review (8 month clock), with an Action Date under the PDUFA program of April 29, 2017. The Team did not have any filling issues to discuss at this point in time.

3. Potential Consults Status

Discussion: The following consult requests were uploaded in DARRTS: OPDP, DMPP, OSI, OSE, and QT-IRT. The Team briefly discussed clinical site and manufacturing inspections scheduled. The Team also discussed the status of obtaining Special Government Employee (SGE). Currently three medical oncologists specializing in thoracic/lung cancer have been approached and is pending addition to the general SGE list with the intent of participating in the review of this application. A patient consultant, who is an existing SGE, was also approached. The Team briefly discussed the need for CDRH consult and determined that CDRH, as well as DPMH, LDT and PeRC consults, were not needed. The Team determined that no other consults were needed.
4. Upcoming / TBD Internal Team Meetings

**Discussion:** The Team briefly discussed the next scheduled internal meeting, the Filing meeting scheduled on October 3, 2016. The Team was reminded to bring Filing reviews and interim deliverables, and be prepared to identify significant filing issues. The Team was provided a link to applicable templates. Additionally, the labeling meeting schedule was briefly discussed. The Team was provided a link to the Applicant’s proposed package insert and patient information. The carton and container labeling location in EDR was provided. The Team also confirmed the need for monthly Team meetings.

The Team briefly discussed the clinical pharmacology PMRs discussed during the pre-NDA meeting held back in April 15, 2016 and determined that separate PMC/PMR meetings were not necessary at this point in time. The Team confirmed that no additional PMRs/PMCs have been identified at this point in time.

5. Application Orientation Meeting:

**Discussion:** The Team briefly discussed the Application Orientation meeting scheduled for October 21, 2016. The Team was reminded that the Outlook invite was sent as a placeholder, and the RPM will send out a webex link ahead of the meeting for remote access. The core disciplines are expected to attend the meeting in person.

The Team was reminded that following the Application Orientation meeting, a Dataset Orientation meeting will be held to discuss clinical and statistical datasets. All other disciplines were invited as FYI.

6. ODAC

**Discussion:** The Team discussed that an ODAC is not required at this point in time, as the application does not raise significant safety or efficacy issues at this point in time.

7. Standing Meetings with Applicant

**Discussion:** The Team discussed that standing tcons with the Applicant are not needed at this point in time.

8. MISC Items or Issues

**Discussion:** The Team discussed that this application will be under the shared review pilot, which pertains to the core review disciplines only (except CMC Review Team). Additional information will be provided to the Team as the application review progresses.

The Team also stated that the need for a press release or an ASCO burst will be discussed at the next Administrative Rounds.
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/s/

LEAH S HER
09/20/2016
Memorandum

DATE:        September 20, 2016

FROM:        Martha Donoghue, M.D.
             Associate Director (Acting)
             Division of Oncology Products 2
             Office of Hematology and Oncology Products
             Office of New Drugs
             Center for Drug Evaluation and Research

SUBJECT:     Review Designation memo

Sponsor:     ARIAD Pharmaceuticals Inc.

Product:     brigatinib tablets, 30 and 90 mg

Proposed Indication: Brigatinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

TO:          NDA 208772

The review status of this file submitted as a New Molecular Entity original NDA is designated to be:

☐ Standard (12 Months) ☒ Priority (8 Months)

BACKGROUND

Brigatinib is a tyrosine kinase inhibitor that targets ALK, ROS1, and insulin-like growth factor 1 receptor (IGF-1R). In this NDA, ARIAD Pharmaceuticals provided clinical data from Studies AP26113-13-201 and AP26113-11-101 to support the efficacy of brigatinib in patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Study AP26113-11-101 was a multicenter, single arm two-part dose-escalation trial with expansion cohorts conducted to assess the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of brigatinib. Patients enrolled...
in the dose-finding portion of the trial included those with advanced malignancies except leukemia. The second part of the trial comprised the following five expansion cohorts defined by tumor histology and molecular characteristics in addition to prior therapeutic exposure: ALK+ NSCLC patients who were naïve to ALK-targeted therapies (Cohort 1) or had resistance to crizotinib (Cohort 2); NSCLC patients whose tumors exhibited an EGFR-T790M mutation and who were resistant to one prior EGFR inhibitor (Cohort 3); patients with any cancers with abnormalities in ALK, EGFR, ROS1, or other targets against which brigatinib is active (Cohort 4); and ALK+ NSCLC patients with active brain metastases who were naïve or resistant to crizotinib (Cohort 5). The trial enrolled a total of 137 patients across 9 centers in the US and Spain. A total of 128 patients had NSCLC, including 79 patients who had tumors with rearrangements in ALK, and 4 with rearrangements in ROS1. A total of 71 of 79 (89.9%) had been previously treated with crizotinib.

Study AP26113-13-201 was a randomized, open-label, international, multicenter trial that enrolled 222 adult patients with locally advanced or metastatic ALK-positive NSCLC that had progressed on crizotinib. Eligibility criteria permitted enrollment of patients with a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test; ECOG Performance Status of 0-2; and central nervous system (CNS) metastases, provided they were neurologically stable and did not require an increasing dose of corticosteroids. Patients with a history of pulmonary interstitial disease or drug-related pneumonitis were excluded from enrollment. Patients were randomized in a 1:1 ratio to receive brigatinib either at a dose of 90 mg once daily (90 mg regimen, n=112) or 180 mg once daily with a 7-day lead-in at 90 mg once daily (180 mg regimen, n=110). The median duration of follow-up was 8 months. The primary efficacy endpoint was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by the investigator. Additional efficacy endpoints included confirmed ORR as evaluated by an Independent Review Committee (IRC); time to response; progression free survival (PFS); duration of response (DOR); and intracranial ORR, intracranial DOR and intracranial PFS as evaluated by an IRC. Randomization was stratified by brain metastases (present, absent) and best prior response to crizotinib therapy (complete or partial response, any other response/unknown).

Table 1, adapted from the Applicant’s submission, provides a summary of the objective response rate (ORR) and duration of response as assessed by the Investigator for Studies AP26113-13-201 and AP26113-11-101.
### Table 1: Investigator Assessed Response Rate and Duration of Response in Brigatinib Studies

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>AP26113-11-101</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 mg QD (N=13)</td>
<td>90 mg QD → 180 mg QD (N=25)</td>
</tr>
<tr>
<td>Confirmed ORR n (%)</td>
<td>7 (54)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>95%/97.5% CI (^a)</td>
<td>25, 81</td>
<td>55, 91</td>
</tr>
<tr>
<td>Confirmed CR</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>10 (77)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Median DoR (months)</td>
<td>11 (4,17)</td>
<td>15 (8, NR)</td>
</tr>
</tbody>
</table>

\(^a\) CI expressed as 97.5% CI for Study AP26113-13-201 and 95% CI for Study AP26113-11-101

Source: Adapted from Applicant’s submission

Of the 164 (74%) randomized patients who had prior exposure to chemotherapy in Study AP26113-13-201, 79 (48.2%, 95% CI: 40, 56) had a confirmed objective response.

ORR (95% CI) according to IRC assessment for Study AP26113-13-201 was similar to Investigator-assessed ORR [48% (39-58) in the 90 mg QD arm and 53% (43-62) for the 180 mg QD regimen]. The median (95% CI) duration of response (DoR) according to IRC assessment was 14 months (7-NE) in the 90 mg QD arm and 14 months (9 – NE) in the 180 mg QD arm.

**ASSESSMENT OF REQUEST**

In evaluating the review designation for ARIAD’s New Drug Application (NDA), I considered their rationale including the summary results of Studies AP26113-13-201 and AP26113-11-101 and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)

As stated in these FDA documents, an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications.
On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers available therapy (and the terms existing treatment and existing therapy) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication.

FDA’s available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment:
This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: The drug treats a serious condition

Anaplastic lymphoma kinase (ALK) mutation-positive lung cancer accounts for approximately 5% of non-small cell lung cancers (NSCLC), which constitute
approximately 85% of the 224,390 new cases of lung cancer estimated to occur in 2016 by the National Institute of Health (NIH) Surveillance, Epidemiology and End Results (SEER) Program. The estimated US incidence of ALK mutation-positive NSCLC is approximately 9500 new cases of annually. The estimated 5-year survival rate for metastatic lung cancer is less than 5% and there is no evidence that the presence of ALK mutations confer a better prognosis. However, with the advance of effective therapy inhibiting kinase activation, specifically crizotinib, progression-free survival is improved as compared to first-line, platinum-based doublet chemotherapy [HR 0.45 (0.35, 0.60); median PFS 10.9 vs. 7.0 months] or second-line pemetrexed or docetaxel [HR 0.49 (0.37, 0.64); median PFS 7.7 vs. 3.0]. The median survival was 20.8 months for those receiving crizotinib as second-line therapy.

I concur that the indicated population has a serious, life-threatening condition.

Criterion 2: The drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

FDA approved therapy for the second-line treatment of NSCLC that have been evaluated in patients with ALK mutation-positive NSCLC:

- Docetaxel or pemetrexed as second-line chemotherapy following platinum-based doublet chemotherapy. In patients with ALK-mutation-positive NSCLC receiving second-line therapy in a randomized trial comparing the efficacy of platinum-based chemotherapy with crizotinib, demonstrated an ORR of 20% (14, 26) with a median duration of response of 5.6 months.

The following drugs are FDA-approved regimens for the second-line treatment of NSCLC.

- Ramucirumab with docetaxel has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with NSCLC receiving second-line chemotherapy, after platinum-based doublet chemotherapy, the ORR was 23% (95% CI: 20, 26) in patients randomized to ramucirumab plus docetaxel and 14% (95% CI: 11, 17) in patients receiving placebo plus docetaxel.

5 http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202570s014lbl.pdf.
6 http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf
7 http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202570s017lbl.pdf

Reference ID: 3988417
• Nivolumab has not been evaluated in studies of ALK mutation-positive NSCLC. In studies of patients with metastatic squamous NSCLC who experienced disease progression during or after one prior platinum doublet-based chemotherapy, the ORR was 19% (95% CI: 15, 24) in patients randomized to nivolumab and 12% (95% CI: 9, 17) in patients randomized to docetaxel.

FDA granted accelerated approval for the following two drugs for the treatment of patients with ALK-mutation-positive NSCLC who are no longer responding to or are intolerant of crizotinib:

• Ceritinib, which is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib

• Alectinib, which is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

Both ceritinib and alectinib were approved under the provisions of 21 CFR 314 Subpart H; therefore, both drugs are not considered to be available therapy because the clinical benefit of the durable objective response rates observed with ceritinib and alectinib has not been verified.

NCCN Practice Guidelines: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend ceritinib and alectinib for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on crizotinib.

As noted in FDA’s Guidance for Industry (referenced above) “Generally, if there is an available therapy (see section III.B.), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug’s ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy.”

Brigatinib was not compared directly to FDA-approved therapy in clinical trials, however based on data from two multicenter trials, brigatinib has demonstrated a numerically higher response rate (ORR) than was demonstrated in clinical trials reviewed by FDA for other drugs approved broadly for the second-line treatment of NSCLC (i.e., docetaxel alone or with ramucirumab, pemetrexed, and nivolumab). Specifically, the lower bound of the 95% confidence limit around the observed ORRs for brigatinib excludes the upper bound of the 95% confidence limit around the observed ORRs for these second-line treatment regimens. Additionally, data provided by the Applicant indicate that the responses achieved by brigatinib are durable. Based on these data, I conclude that brigatinib provides a significant improvement in a clinically important and durable overall response rate as compared to that demonstrated

8 http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125477s011lbl.pdf
in clinical studies of nivolumab, docetaxel, docetaxel plus ramucirumab, and pemetrexed.

**Recommendation: Priority review.** Based on my preliminary review of the clinical data provided by the Applicant, I have concluded that brigatinib is a drug intended to treat a serious condition and that if approved, brigatinib would provide a significant improvement over available therapy for the treatment of patients with anaplastic lymphoma (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Therefore, I recommend that priority review be granted for this NDA.

{See appended electronic signature page}

Martha Donoghue, M.D.
Acting Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

LEAH S HER
09/20/2016

MARTHA B DONOGHUE
09/20/2016
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

We have the following request for information. Please provide your response via email by 10 AM (EST) Thursday, September 15, 2016 or sooner if possible, and follow that with a formal submission to the NDA.

Comments:

1. Please provide the full name, title, and contact information for the authorized contact for the following organization identified in your NDA application:

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
09/14/2016
NDA 208772

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

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: ALUNBRIG (brigatinib) Tablets, 30 and 90 mg

Date of Application: August 29, 2016

Date of Receipt: August 29, 2016

Our Reference Number: NDA 208772

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 October 28, 2016, in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

If you have any questions, call Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Monica L. Hughes, M.S.  
Chief, Project Management Staff  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research
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/s/

MONICA L HUGHES
09/13/2016
Memorandum

Date: September 13, 2016

From: Leah S. Her, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: NDA 208772 – ARIAD Pharmaceuticals, Inc.
Clinical Pharmacology Review Comments and Information Request

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Alunbrig (brigatinib) tablets, 30 and 90 mg.”

The Clinical Pharmacology Reviewer has the following request for information. Please provide your response via email by 4 PM (EST) on Wednesday, September 21, 2016 or sooner if possible, and follow that with a formal submission to the NDA.

Comments:

1. Submit the analysis datasets and analysis programs (if applicable) associated with the following reports:
   a. "Population Pharmacokinetic Analysis of Brigatinib Based on Phase 1 and Phase 2 PK Data"
   b. "Analyses of the Relationship between Brigatinib Exposure and Selected Safety and Efficacy Outcomes"
   c. "Exposure Response Analyses of Brigatinib in the ALTA study (AP26113-13-201)"

If the requested items have been submitted, please direct us to the folder of the submission package.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
09/13/2016
Dear Ms. Huang:

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

We also refer to your August 19, 2016, correspondence requesting an application orientation meeting to discuss brigatinib. We will consider this an informal Type C Meeting and a meeting minutes will not be issued.

The meeting is scheduled as follows:

**Date:** Friday, October 21, 2016
**Time:** ~1:00 – 2:30 PM (EST)
**Location:** White Oak Building 22, Conference Room: 2205
Silver Spring, MD 20903

Please email me a list of your meeting participants so that their names can be entered into the LobbyGuard system. For each foreign visitor, complete and email me the enclosed FDA Foreign Visitor Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA’s Lobbyguard system. If you receive this email, bring it with you to expedite your group’s admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: **Leah Her 240-402-6611**
Please refer to the following link for visiting the White Oak Campus:
http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/ucm241748.htm

Please submit desk copies and/or slides to Leah Her at the following address:

Leah Her  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 2315  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
Use zip code 20903 if shipping via United States Postal Service (USPS).  
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

If you have any questions, call me (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.  
Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
FDA Foreign Visitor Request Form
| **VISITORS FULL NAME (First, Middle, Last)** |  |
| **GENDER** |  |
| **COUNTRY OF ORIGIN/CITIZENSHIP** |  |
| **DATE OF BIRTH (MM/DD/YYYY)** |  |
| **PLACE OF BIRTH (city and country)** |  |
| **PASSPORT NUMBER:** |  |
| **COUNTRY THAT ISSUED PASSPORT:** |  |
| **ISSUANCE DATE:** |  |
| **EXPIRATION DATE:** |  |
| **VISITOR ORGANIZATION/EMPLOYER** |  |
| **MEETING START DATE AND TIME** | October 21, 2016 / ~1:00 PM (EST) |
| **MEETING ENDING DATE AND TIME** | October 21, 2016 / ~2:30 PM (EST) |
| **PURPOSE OF MEETING** | Application Orientation Meeting |
| **BUILDING(S) & ROOM NUMBER(S) TO BE VISITED** | ~1:00 – 1:30 PM (EST): WO 22 Room 1309  
~1:30 – 2:30 PM (EST): WO 22 Room 2205 |
| **WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?** | No |
| **POINT OF ENTRY**  
(This is the building that the foreign visitor will enter) | WO 22 |
| **HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)** | Leah Her, RPM  
WO 22 Room 2315  
240-402-6611 |
| **ESCORT INFORMATION (If different from Hosting Official)** | Same as above |
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/s/

LEAH S HER
09/09/2016
NDA 208772

ARIAD Pharmaceuticals, Inc.
26 Landsdowne Street
Cambridge, MA 02139-4234

ATTENTION: Guilin Huang, MBA, RAC
Associate Director, Regulatory Affairs

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated and received August 29, 2016, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brigatinib, tablets, 30 mg and 90 mg.

We also refer to your correspondence, dated and received June 16, 2016, requesting review of your proposed proprietary name, Alunbrig.

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

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

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

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
  (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4901. For any other information regarding this application, contact Leah Her, Regulatory Project Manager in the Office of New Drugs, at 240-402-6611.

Sincerely,

(See appended electronic signature page)

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

LUBNA A MERCHANT on behalf of TODD D BRIDGES
09/09/2016
ACKNOWLEDGE PRESUBMISSION

ARIAIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

We have received the second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ALUNBRIG (brigatinib) Tablets, 30 and 90 mg

Date of Submission: July 28, 2016

Date of Receipt: July 28, 2016

Our Reference Number: NDA 208772

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

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application.

We acknowledge that you are using the FDA Electronic Submissions Gateway (ESG) for your submissions to NDA 208772.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

LEAH S HER
08/08/2016

Reference ID: 3969621
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for “Alunbrig [Proposed] (brigatinib).”

We also refer to your July 28, 2016, amendment, containing the second portion of the rolling submission.

The Product Quality Reviewer has the following request for information. Please provide your response to via email by 4 PM (EST) on Monday, August 15, 2016 or sooner if possible, and follow that with a formal submission to the NDA.

Comments:

1. Please provide an updated letter of authorization for Drug Master File (DMF) that clearly identifies that the DMF holder is providing right of reference to ARIAD pharmaceuticals in support of this NDA.

If you have any questions, please contact me at leah.her@fda.hhs.gov or at (240) 402-6611.
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/s/

LEAH S HER
08/08/2016
ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

Please refer to your second section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for “Alungbrig [Proposed] (brigatinib).”

Our OSI Reviewer has the following request for information. Please provide your response to your assigned Regulatory Project Manager, Ms. Leah Her, via email no later than noon on Tuesday, August 9, 2016, and follow that with a formal submission to the NDA.

Comments:

1. We have received your Summary Level Clinical Site Dataset for Study AP26113-13-201 and have been unable to process the data submitted. We are providing the following link to provide you with the most recent Office of Scientific Investigations instructions to assist with formatting your dataset:

   We ask that you provide a revised dataset (within five business days) that includes:
   a. Number of subjects screened at each site
   b. Financial Disclosure Information (FINLMAX and FINLDISC as in Appendix 1 of attached Specifications) - financial disclosure information in the tool is voluntary. If unavailable or unable to retrieve, please set to "-1").

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721) or your assigned Regulatory Project Manager, Ms. Leah Her at leah.her@fda.hhs.gov or (240-402-6611).
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/s/

MEREDITH LIBEG
08/02/2016
NDA 208772

ACKNOWLEDGE PRESUBMISSION

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ALUNGBRIG (brigatinib) Tablets, 30 and 90 mg
Date of Submission: June 16, 2016
Date of Receipt: June 16, 2016
Our Reference Number: NDA 208772

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

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application.

We acknowledge that you are using the FDA Electronic Submissions Gateway (ESG) for your submissions to NDA 208772.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

LEAH S HER
06/28/2016

Reference ID: 3952034
Dear Ms. Huang:

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

We also refer to your April 25, 2016 request for rolling submission and review of portions of your planned New Drug Application (NDA) for brigatinib which was designated as a breakthrough therapy in the letter dated October 1, 2014 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib, as follows:

- **1st Portion:** The June 2016 submission will include most of Module 1 Regional/Administrative Information (except for a risk management plan [RMP] and proposed labeling); all of Module 4 Nonclinical Study Reports and all pertinent nonclinical information in Module 2 (Nonclinical Overview and Nonclinical Summary sections) will also be submitted.

- **2nd Portion:** The July 2016 submission will include establishment and clinical site information, letters of authorization, and the environmental analysis in Module 1; all pertinent Quality Overall Summary information in Module 2; all of Module 3 Quality (CMC) information; and the BIMO summary level clinical site dataset in Module 5.

- **3rd and Final Portion:** The August 2016 submission will include all of Module 5 Clinical Study Reports, including all clinical and statistical sections including clinical pharmacology exposure-response analyses from Study AP26113-13-201, the RMP, all pertinent Clinical Overview and Clinical Summary information (Module 2), and the remaining Regional/Administrative Information (Module 1) including proposed labeling which will include patient prescribing information and carton and container labeling.

We have reviewed and accept your request and plan for submitting portions of the proposed application.
If the breakthrough therapy designation for brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib is rescinded, submission of portions of the NDA will not be permitted under this program.

For further information regarding breakthrough therapy designations, please refer to the FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics\(^1\).

If you have any questions, contact Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

STEVEN J LEMERY on behalf of PATRICIA KEEGAN
05/25/2016

Reference ID: 3934984
IND 110935

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Huang:

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

We also refer to the telecon between representatives of your firm and the FDA on April 15, 2016. The purpose of the meeting was to discuss the contents and format of the initial New Drug Application (NDA) for brigatinib as a treatment for patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

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

If you have any questions, call me at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 15, 2016 / 2:30 – 3:30 PM (EST)
Meeting Location: Teleconference

Application Number: 110935
Product Name: brigatinib
Indication: Treatment of patients with metastatic anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Sponsor/Applicant Name: ARIAD Pharmaceuticals Inc.

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Leah Her

FDA ATTENDEES
Steven Lemery Associate Director (Acting), DOP2
Gideon Blumenthal Clinical Team Lead, DOP2
Dickran Kazandjian Clinical Reviewer, DOP2
Margit Horiba Clinical Reviewer, DOP2
Damiette Smit Clinical Reviewer, DOP2
Meredith Libeg Senior Regulatory Health Project Manager, DOP2
Leah Her Regulatory Health Project Manager, DOP2
Whitney Helms Nonclinical Supervisor, DHOT
Jeanne Fourie Zirkelbach Clinical Pharmacology Team Lead, DCPV
Sirisha Mushhi Statistical Reviewer, DBV

SPONSOR ATTENDEES
Paris Panayiotopoulos President and Chief Executive Officer
Daniel Bollag Senior Vice President, Regulatory Affairs and Quality
Andrew Slugg Vice President, Regulatory Affairs
Guilin Huang Associate Director, Regulatory Affairs
Shreya Mehta Senior Associate, Regulatory Affairs
David Kerstein Senior Medical Director, Clinical Research & Development
Ronald K. Knickerbocker Vice President, Biomedical Data Sciences & Information
Narayana I. Narasimhan Vice President, DMPK and Preclinical Safety

Reference ID: 3919390
BACKGROUND

ARIAD is planning to submit a New Drug Application (NDA) for brigatinib for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib under the accelerated approval pathway (21 CFR Subpart H).

On February 12, 2016, ARIAD submitted a meeting request to discuss the contents and format of the NDA. The meeting request was granted on February 24, 2016, as a Type B meeting. The meeting packages were received on March 16, 2016. The updated top-line results from Study AP26113-13-201 (ALTA trial) were received on April 4, 2016.

Brief Regulatory History:

- May 24, 2011 – pre-IND meeting held to discuss the first-in-human (FIH) trial of AP26113, Protocol AP26113-11-01, entitled “A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113,” and the overall development of brigatinib for the treatment of cancer patients with ALK rearrangements or endothelial growth factor (EGF) receptor mutations
- July 26, 2011 – New IND containing Protocol AP26113-11-01, received on June 28, 2011, was allowed to proceed
- February 12, 2013 –
- March 18, 2013 – End of Phase 1 (EOP1) meeting held to discuss the proposed clinical development program for brigatinib that will support an NDA for the treatment of patients with metastatic NSCLC with ALK rearrangements who have experienced failure of prior crizotinib therapy
- October 22, 2013 – Preliminary comments issued for a Pre-Phase 3 meeting to discuss Study AP26113-13-201 that ARIAD intends to use to support marketing applications; ARIAD requested the meeting to be withdrawn after receipt of the preliminary comments
- October 24, 2013 – Correspondence issued to clarify clinical pharmacology advice in the October 22, 2013, preliminary comments
• October 1, 2014 – Breakthrough designation request granted for brigatinib for the
treatment of patients with ALK-positive NSCLC whose tumors are resistant to crizotinib
• June 30, 2015 – Initial Comprehensive Multi-Disciplinary Breakthrough Therapy
  meeting held to discuss the brigatinib development program
  
  
• October 30, 2015 – Correspondence issued to clarify that although ARIAD’s proposed
early onset pulmonary events case review and a proposed case definition were
acceptable, ARIAD should also assess for the overall incidence of pneumonitis based on
a broader definition; ARIAD’s revised adverse case review report submitted on March
10, 2016, was reviewed and found to be acceptable
• November 16, 2015 – Conditional acceptance granted for the proposed proprietary name
of ALUNBRIG; FDA stated that ARIAD should submit a request once the NDA is
submitted
• February 22, 2016 – Correspondence issued to provide an assessment of the ECG data
from study AP26113-11-101; FDA stated that although the overall ECG data acquisition
and interpretation appears acceptable, a thorough QT study in healthy subjects may be
feasible as brigatinib was studied in healthy subjects

Refer to the minutes of March 2, 2016 pre-NDA/CMC-only meeting for CMC-specific related
background information and discussion.

In addition, a request for an orphan designation request for brigatinib in ALK-positive or c-ros
oncogene 1 (ROS1)-positive NSCLC is currently under review in the Office of Orphan Products
Development (OOPD).

Product Information
Brigatinib (also known as AP26113) is a tyrosine kinase inhibitor (TKI) that targets activated
mutant forms of ALK and ROS1. ARIAD states that the initial NDA will include brigatinib in
two white film-coated tablet strengths, 30 and 90 mg, with the following compendial grade
excipients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate,
hydrophobic colloidal silica, magnesium stearate, plus the film coat. The tablets will be
packaged in high density polyethylene bottles with 1 g cap. Brigatinib will be administered orally. ARIAD intends to file the NDA with two
drug substance manufacturers, and two drug product manufacturers, Penn Pharmaceutical Services Ltd.

Non-Clinical
ARIAD states that they have conducted nonclinical pharmacology (in vitro and in vivo), safety
(cardiovascular, respiratory, central nervous, and renal), ADME and pharmacokinetic (PK) drug
interactions studies, 28-day repeat dose toxicology studies in rats and Cynomolgus monkeys, in
vitro and in vivo genotoxicity studies, and a phototoxicity study in rats. Six month GLP-
compliant toxicity studies in rats and monkeys, as well as embryofetal development toxicity
study in rats are underway and planned for inclusion in the NDA submission. ARIAD proposes
using the impurity levels from the toxicology batch to justify their specifications and to use the
approach recommended in ICH M7 to justify any genotoxic impurities.
Clinical

AP26113-11-101 (Study 101)
This is a first-in-human, open-label, multicenter, dose-escalation (3+3 design) study of the safety, tolerability, PK, and preliminary antitumor activity of brigatinib. Enrollment completed in July 2014, with a total of 137 patients. The “phase 2” portion included 5 cohorts which were histologically and molecularly defined: patients with ALK-positive NSCLC who are naive to ALK-targeted therapies (Cohort 1) or have resistance to crizotinib (Cohort 2); patients with NSCLC with activating mutations in EGFR that have resistance to a prior EGFR inhibitor (Cohort 3); patients with any cancers with abnormalities in ALK, EGFR, ROS1, or other targets against which brigatinib is active (Cohort 4); and patients with ALK-positive NSCLC with active brain metastases who are naive or resistant to crizotinib (Cohort 5). Activity is being measured by objective response rate (ORR), which is evaluated by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. In patients treated with prior crizotinib, 51/71 had a response (71.8% ORR), 44 of which were confirmed. Of the 8 crizotinib-naive patients, 100% had a confirmed response.

AP26113-13-201 (ALTA)
This is a pivotal randomized, multicenter, international study of brigatinib in patients with ALK-positive NSCLC who previously progressed on crizotinib. Patients (N=222) with ALK-positive NSCLC who progressed on crizotinib were randomized 1:1 to receive brigatinib in one of two different dosing regimens: (1) Arm A; 90 mg QD, continuously, or (2) Arm B; 90 mg QD for 7 days, then 180 mg QD, continuously (90 mg QD → 180 mg QD). Eligible patients were to have histologically or cytologically confirmed locally advanced or metastatic NSCLC with a historical documentation of ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or documented ALK-positivity by a different test and tissue available for the Vysis® FISH test. Patients were required to have progressive disease while on crizotinib. The primary endpoint of this study is confirmed ORR as assessed by the investigator, per RECIST v 1.1.

The study completed in September 2015. Treatment and follow-up is ongoing. ARIAD plans to include analyses of safety and efficacy based on a data extraction date of February 29, 2016, for the initial NDA. Additional safety data and limited efficacy data based on a data extraction date of May 31, 2016, will be provided within 60 days and 30 days after the initial NDA submission, respectively. As of December 07, 2015, 112 patients were randomized into Arm A (90 mg QD) and 110 patients were randomized into Arm B (90 mg QD for 7 days, followed by continuous dosing at 180 mg QD). The median age was 50.5 and 56.5 years, and 71.4% and 67.3% of patients had brain metastases at baseline in Arms A and B, respectively. In both arms, approximately 74% of patients had received prior chemotherapy. Of the 222 enrolled patients, 218 (98.2%) had study drug administration data entered into the clinical database. One additional patient is known to have taken at least 1 dose of brigatinib, but study drug administration data was pending at the time of the current database extraction. Three additional
patients are known to have been randomized but never treated. All 222 patients are included for efficacy analyses; however, only 218 patients are included in the Treated Population for the safety analyses.

At the time of data extraction, 33.0% and 26.4% of patients in Arms A and B, respectively, had discontinued treatment. The median time on treatment was 5.7 and 5.3 months in Arm A and Arm B, respectively. Investigator-assessed confirmed ORR in Arm A was 34.8% (39/112); including 1 complete response (CR), with 12 additional single responses awaiting confirmation at the time of the data extraction. In Arm B, investigator-assessed confirmed ORR was 44.5% (49/110), including 5 CRs, with 10 additional single responses awaiting confirmation at the time of the data extraction.

Discontinuation due to adverse events (AEs) occurred in 2.7% of patients in Arm A and 6.4% of patients in Arm B. The most common Grade $\geq 3$ treatment-emergent AEs in Arm A included hypertension (3.7%), pneumonia (2.8%), dyspnea (2.8%), increased lipase (2.8%), decreased neutrophils (2.8%), and blood creatine phosphokinase increased (2.8%). The most common Grade $\geq 3$ treatment-emergent AEs in Arm B included blood creatine phosphokinase increased (8.2%), hypertension (5.5%), pneumonia (4.5%), rash (3.6%), and pneumonitis (all in the first 7 days at 90 mg) (2.3%). Early onset pulmonary events (EOPE) (within the first 7 days of treatment) occurred in 14 (6.4%) patients [7 (3.2%) patients Grade $\geq 3$]; no such events occurred during the first 14 days after escalation to 180 mg in Arm B. Three additional patients experienced a later onset pneumonitis-like event: 1 with Grade 3 pneumonitis (at 180 mg QD), and 2 with Grade 2 pneumonitis (at 90 mg QD and 180 mg QD, respectively). Overall, 17/218 (8.2%) patients in the ALTA trial experienced an EOPE or later onset pneumonitis-like event.

ARIAD also submitted the following updated results using a February 29, 2016 extraction date:

### Table 1

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Arm A 90 mg QD</th>
<th>Arm B 90 mg QD $\rightarrow$ 180 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>112</td>
<td>110</td>
</tr>
<tr>
<td>Confirmed Investigator-Assessed Objective Response, n (%) (97.5% CI)</td>
<td>50 (44.6) (34.0-55.6)</td>
<td>59 (53.6) (42.6-64.5)</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>13.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Median PFS, months, (95% CI)</td>
<td>9.2 (7.4-15.6)</td>
<td>12.9 (11.1-NE)</td>
</tr>
<tr>
<td>Events</td>
<td>50/112</td>
<td>31/110</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.55 (0.35 – 0.86)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>Not Reached, (NE)</td>
<td>Not Reached, (NE)</td>
</tr>
<tr>
<td>Events</td>
<td>27/112</td>
<td>17/110</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.57 (0.31-1.05)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 90 mg QD $\rightarrow$ 180 mg QD = 90 mg QD for 7 days, followed by continuous dosing at 180 mg QD, NE = not estimable

Data extraction date: 29 February 2016
NDA data package
ARIAD plans to submit a rolling NDA beginning in late-June 2016 for brigatinib for the proposed indication under the accelerated approval regulations: treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

**Table 4**  Treatment Exposure (Treated Population)

<table>
<thead>
<tr>
<th></th>
<th>Arm A 90 mg QD N=108</th>
<th>Arm B 90 mg QD → 180 mg QD N=110</th>
<th>Total N=218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Exposure (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>229.0</td>
<td>238.5</td>
<td>236.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>1.0, 508.0</td>
<td>2.0, 615.0</td>
<td>1.0, 615.0</td>
</tr>
<tr>
<td><strong>Dose Intensity (mg/day)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>90.0</td>
<td>174.1</td>
<td>97.6</td>
</tr>
<tr>
<td>Min-Max</td>
<td>58.7-171.0</td>
<td>38.6-179.1</td>
<td>38.6-179.1</td>
</tr>
<tr>
<td><strong>Relative Dose Intensity(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
<td>98.2</td>
<td>99.5</td>
</tr>
<tr>
<td>Min-Max</td>
<td>50.0-190.0</td>
<td>3.8-101.2</td>
<td>3.8-190.0</td>
</tr>
</tbody>
</table>

Abbreviations: 90 mg QD → 180 mg QD = 90 mg QD for 7 days, followed by continuous dosing at 180 mg QD

1 Observed total dose divided by expected total dose which is defined as planned dose (according to arm) multiplied by the number of dosing days times 100
2 Note: patients in Arm A were allowed to escalate to 180 mg QD at disease progression

Data extraction date: 29 February 2016

**Table 3**  Brigatinib Clinical Trials in ALK+ NSCLC Patients to be Included in the NDA Submission

<table>
<thead>
<tr>
<th></th>
<th>AP26113-13-201 (ALTA)</th>
<th>AP26113-11-101 (Study 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Phase 2, randomized, open label study comparing 2 doses</td>
<td>Phase 1/2, single arm, open label study</td>
</tr>
<tr>
<td><strong>Key Objectives</strong></td>
<td>Evaluate the efficacy (systemic and intracranial), safety and tolerability</td>
<td>Determine the safety profile of brigatinib (MTD, DLTs); evaluate the RP2D, PK profile, and preliminary anti-tumor activity</td>
</tr>
</tbody>
</table>
| **Patient Population**         | 222 patients with ALK+ NSCLC
Arm A (90 mg QD): N=112
Arm B (90 mg QD for 7 days, followed by continuous dosing at 180 mg QD): N=110 | 137 patients, 79 patients with ALK+ NSCLC (71 of which had prior treatment with crizotinib) |
| **Investigational sites**      | 94 investigational sites throughout the US, EU, and Asia | 9 investigational sites (8 US, 1 EU) |
| **Dosing**                     | 90 mg QD (Arm A), 90 mg QD → 180 mg QD (Arm B) | Phase 1: 3+3 dose escalation (30 mg daily to 300 mg daily)
Phase 2: 3 doses were tested
  • 90 mg QD,
  • 90 mg QD → 180 mg QD
  • 180 mg QD |

Reference ID: 3919390
## Proposed rolling NDA submission plan

ARIAD proposes a rolling submission in three parts comprising the nonclinical, CMC, and clinical NDA sections, in that order. ARIAD is also proposing the submission of updated stability data and a limited set of efficacy data within the 30-day period after the last rolling NDA submission as minor components per PDUFA V. Finally, a safety update complying with 21 CFR 3 14.50(d)(5)(vi)(a) is proposed for submission 60 days after the final rolling NDA submission.

### Table: Study Period and Data Available For NDA Meeting

<table>
<thead>
<tr>
<th>Study Period</th>
<th>AP26113-13-201 (ALTA)</th>
<th>AP26113-11-101 (Study 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First patient dosed</td>
<td>June 2014</td>
<td>Sept 2011</td>
</tr>
<tr>
<td>Last patient first dose</td>
<td>Sept 2015</td>
<td>July 2014</td>
</tr>
</tbody>
</table>

| Study Status | 152 patients ongoing as of 07 December 2015 | Ongoing (N=42 overall, N=36 ALK+ NSCLC) as of 16 November 2015 |

<table>
<thead>
<tr>
<th>Data Cut-off and Data Available For Pre-NDA Meeting</th>
<th>07 December 2015</th>
<th>16 November 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (222) patients enrolled</td>
<td>All (137) patients enrolled</td>
<td></td>
</tr>
<tr>
<td>Minimum potential follow-up: 2.6 months, median follow-up: 6.5 months</td>
<td>Minimum potential follow-up: 16.0 months</td>
<td></td>
</tr>
<tr>
<td>Median (range) exposure: 5.5 months (1 day – 17.5 months)</td>
<td>Median (range) exposure: 7.5 months (1 day – 44.4 months) overall, 17.0 months (1 day – 44.4 months) for ALK+ NSCLC patients</td>
<td></td>
</tr>
<tr>
<td>152 (68.5%) patients ongoing</td>
<td>36 (45.6%) of ALK+ NSCLC patients ongoing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Cut-off and Data Available For Initial NDA Submission</th>
<th>29 February 2016</th>
<th>16 November 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum potential follow-up: 5.3 months</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Projected median follow-up: 8.7 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A potential(^a) of 78% patients with ≥6 months follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A potential(^a) of 23% patients with ≥12 months follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Cut-off and Data Available For 30-day Efficacy Update</th>
<th>31 May 2016</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum potential follow-up: 8.3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Projected median follow-up: 11.6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A potential(^a) of 85% patients with ≥6 months follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A potential(^a) of 47% patients with ≥12 months follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Cut-off and Data Available For 60-day Safety Update</th>
<th>31 May 2016</th>
<th>31 May 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as above</td>
<td>Minimum follow-up: 16.0 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Projected median follow-up: 28.3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A potential(^a) of 100% patients with ≥12 months follow-up</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: 90 mg QD → 180 mg QD = 90 mg QD for 7 days, followed by continuous dosing at 180 mg QD; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; PK = pharmacokinetic; RP2D = recommended phase 2 dose
The initial NDA will provide efficacy data from the ALTA trial based on a February 29, 2016, data extraction date and from Study 101 based on a November 16, 2015, data extraction date. ARIAD proposes to provide the following limited set of efficacy endpoints from the ALTA trial based on a data extraction date of May 31, 2016 (90 days after the data extraction for initial NDA submission): investigator-IRC-assessed ORR and duration of response, and IRC-assessed intracranial ORR and duration of response.

Table 5
Minor Clinical Components Submitted within 30 Days after the Initial NDA Submission

<table>
<thead>
<tr>
<th>NDA Update</th>
<th>Proposed Content and Format for NDA Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 30-day efficacy update in September 2016 consists of efficacy data for:</td>
<td>• Addendum to Module 2.7.3 – Summary of Clinical Efficacy to provide a brief summary (e.g., &lt;10 pages) of updated efficacy data from the 31 May 2016 data extraction of ALTA, with supporting statistical tables</td>
</tr>
<tr>
<td>• Investigator-/IRC-assessed ORR and duration of response</td>
<td>• Datasets and appendices</td>
</tr>
<tr>
<td>• IRC-assessed intracranial ORR and duration of response from ALTA</td>
<td>o Cumulative datasets and appendices from ALTA based on 31 May 2016 data cut-off will be provided in the Study Folder of eCTD in Module 5</td>
</tr>
<tr>
<td>• Minimum follow-up: 8.3 months</td>
<td>o Pooled datasets for intracranial efficacy data for Study 101 (data extraction of 16 November 2015) and ALTA (data extraction of 31 May 2016) and appendices for the Addendum of Module 2.7.3 will be provided in Module 5.3.5.3 in Module 5</td>
</tr>
<tr>
<td>• Projected median follow-up: 11 months</td>
<td>• Updated Label – Section 14 of USPI will reflect the updated efficacy data</td>
</tr>
</tbody>
</table>

Note: Module 2.5 and the CSR for ALTA will not be updated.

Table 6
NDA Documents Submitted for the 60-Day Safety Update

<table>
<thead>
<tr>
<th>NDA Update</th>
<th>Proposed Content and Format for Clinical Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-day safety update in October 2016: Consist of updated safety data from both Study 101 and ALTA</td>
<td>• A fully updated version of Module 2.7.4</td>
</tr>
<tr>
<td>• Projected minimum follow-up: 8.3 months</td>
<td>• Cumulative safety datasets, updated narratives, and CRFs based on the 31 May 2016 data extraction for Study 101 and ALTA.</td>
</tr>
<tr>
<td>• Projected median follow-up: 11 months</td>
<td>o Cumulative datasets and appendices from Study 101 based on 31 May 2016 data cut-off will be provided in the Study Folders of eCTD in Module 5</td>
</tr>
<tr>
<td></td>
<td>o Pooled safety databases and appendices for ISS and Module 2.7.4 will be provided in Module 5.3.5.3 of the eCTD.</td>
</tr>
<tr>
<td></td>
<td>o Updated narratives and CRFs will be provided in the respective Study Folders of eCTD in Module 5</td>
</tr>
<tr>
<td></td>
<td>• Updated Label – Section 5 and 6 of USPI will reflect the updated safety data in the 60 day update.</td>
</tr>
</tbody>
</table>

Note: Module 2.5 and the CSRs for Study 101 and ALTA will not be updated.
Proposed Post Marketing Requirements
ARIAD proposes to submit three clinical pharmacology components as post-marketing requirements after NDA approval. These are also the reports and/or results from:

- Hepatic Impairment Study AP26113-15-107
- Renal Impairment Study AP26113-15-108
- Exposure-Analysis Report for ALTA trial

DISCUSSION

Regulatory

1. **Background:** Refer to Company Position on pages 27 to 34 of the Briefing Document.

**Does the Agency agree that the proposed data package is adequate to support the submission of an NDA under the accelerated approval regulations (21 CFR 314 Subpart H) for brigatinib as a treatment for patients with metastatic ALK+ NSCLC who have progressed on or are intolerant to crizotinib?**

**FDA Response:** In general, FDA agrees that the proposed data package is adequate to support the submission of an NDA except for the following:

a. A 30 day efficacy update should not be submitted. If the results from the May 31, 2016, data cut-off are necessary to support the NDA submission, submit those results in the original NDA.


c. Include exposure-response analyses from the ALTA study in the initial NDA submission in order to further support the dosing regimen.

FDA recommends that ARIAD submit the summary results of the IRC analyses to the IND prior to the NDA submission so that FDA can provide advice regarding the acceptability of the proposed data package.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response. ARIAD stated that ARIAD believes that the February 29, 2016 data transfer from ALTA are adequate to support the NDA submission and will not plan to submit the 30 day efficacy update. In addition,
ARIAD agreed to include the exposure-response analyses from the ALTA trial in the initial NDA submission as part of the last rolling submission. ARIAD stated that ARIAD would revise the rolling submission plan accordingly and submit the plan to the IND as a “REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION.” Lastly, ARIAD agreed to submit top-line summary results of IRC analyses (e.g., confirmed objective response rate, duration of response) from the ALTA trial using the February 29, 2016 data transfer to the IND prior to the NDA submission. No discussion occurred at the meeting.

2. **Background:** Refer to Company Position on pages 35 to 46 of the Briefing Document.

Can the Agency please comment on the proposed rolling NDA submission plan, specifically:

a. **Does the Agency agree that the updated schedule and content for the rolling NDA submission are acceptable?**

   **FDA Response:** No, the content for the rolling NDA submission is not acceptable. Please see below.

   **ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and referred FDA to ARIAD’s response to Questions 1a and 1c. No discussion occurred at the meeting.

b. **Does the Agency agree to the content and format of the documents that will be submitted 30 days after the initial NDA to provide updated efficacy data and an updated draft label?**

   **FDA Response:** No, FDA does not agree. The 30 day efficacy update constitutes the major efficacy results; therefore, submit those results at the time of the clinical module submission. Additionally, submit a single efficacy dataset with a single data cut-off.

   **ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

c. **Does the Agency agree to the content and format of the documents that will be submitted 60 days after the initial NDA to provide the updated safety data and an updated draft label?**

   **FDA Response:** While FDA agrees on submission of a 60-day Safety Update, ARIAD should make the following changes to the proposal:

   - Do not submit an updated module 2.7.4; instead provide an addendum to the original module.
The label should not be updated unless a major safety signal (e.g., update to a Warning or Contraindication) is observed in the updated safety data.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

### Nonclinical

3.  **Background:** Refer to Company Position on pages 47 to 50 of the Briefing Document.

**Does the Agency agree that the updated nonclinical data package is adequate to support an NDA submission for the proposed indication?**

**FDA Response:** The completed and ongoing preclinical toxicity studies described in the meeting package appear sufficient to support NDA filing; however a final decision regarding the adequacy of the submitted data to support a regulatory action will be made after the review of the study reports at the time of NDA submission.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

### Clinical

4.  **Background:** Refer to Company Position on pages 51 to 59 of the Briefing Document.

**Can the Agency please comment on ARIAD’s proposed approach to support the recommended dosing regimen for clinical use in the NDA?**

**FDA Response:** In general, FDA agrees that the available data support the proposed dosing regimen of 90 mg daily for 7 days followed by 180 mg daily. However, FDA will make the final determination at the time of NDA submission when all data and analyses are complete.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

5.  **Background:** Refer to Company Position on pages 60 to 62 of the Briefing Document.

**Can the Agency please comment on proposed efficacy analysis plan for the NDA submission?**

**FDA Response:** FDA agrees with ARIAD’s proposal to present efficacy endpoints as side-by-side presentations from each study as part of the NDA submission. ARIAD may choose to present pooled results for intracranial response; however, the results from the individual studies should also be presented side by side.
ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

6. **Background:** Refer to Company Position on pages 63 to 65 of the Briefing Document.

Can the Agency please comment on proposed safety analysis plan for the NDA submission?

**FDA Response:** FDA agrees with the proposed safety analysis plan.

ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

7. **Background:** Refer to Company Position on pages 66 to 67 of the Briefing Document.

Does the Agency agree that the proposed plans for submission of efficacy and safety data meet the requirements for an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS)?

**FDA Response:** FDA agrees with the proposed plans for submission of Module 5 components which appear to follow FDA guidance.

ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

8. **Background:** Refer to Company Position on page 68 of the Briefing Document.

Does the Agency agree that the proposed set of CRF’s and narratives to support the NDA submission?

**FDA Response:** Yes, FDA agrees with the proposal.

ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

9. **Background:** Refer to Company Position on pages 69 of the Briefing Document.

Does the Agency agree that the proposal for the format and content of the electronic datasets to be submitted in the NDA?

**FDA Response:** Yes FDA agrees; however, a final determination will be made upon review of the datasets submitted to the NDA.

Please also submit a one-patient-per-row horizontal dataset incorporating demographics and key efficacy variables including ORR, DoR, by IRR and investigator, intracranial response, and maximum change in percent of target lesions from baseline.
**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s response and stated that no clarification was required. No discussion occurred at the meeting.

**ADDITIONAL COMMENTS**

**Office of Scientific Investigations**

10. In the NDA submission, please provide the 1) general study related and comprehensive clinical investigator information, and the 2) subject level data listing by site. Refer to OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS below for additional information, including the format of the submission.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

**Clinical Pharmacology**

11. In the NDA submission, include specific milestones and timelines for the proposed postmarketing requirements for renal and hepatic impairment studies not anticipated to be completed at the time of submission.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

12. Please confirm that 46.8% and 53.4% inhibition of atorvastatin uptake in OATP1B1 and OATP1B3 vesicles occurred at 120 μM.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

13. In the Summary of Clinical Pharmacology, address the following questions:

   a. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
   b. What are the exposure-safety and exposure-efficacy relationships?
   c. How was the potential for brigatinib to prolong the QT/QTc interval assessed? What are the conclusions and proposed labeling description?
   d. What are the characteristics of absorption, distribution, and elimination?
   e. What are the effects of food on the bioavailability of brigatinib? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
f. What influence do intrinsic factors (such as sex, race, weight, disease, organ impairment) have on brigatinib exposure, efficacy and safety? What dose modifications are recommended?

g. What influence do the extrinsic factors (such as drug interactions, diet) have on brigatinib exposure, efficacy, and safety? What dose modifications are recommended?

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

In addition, apply the following advice in preparing the clinical pharmacology sections of the original NDA submission:

14. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics studies.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

15. Provide complete datasets for all clinical pharmacology and biopharmaceutics studies. The subject’s unique ID in the pharmacokinetic datasets should be consistent with those in datasets submitted for clinical review.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

16. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

17. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

**ARIAD’s Emailed Response of 4/14/16:** ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.
18. Identify individual subjects with dose modifications; the time to the first dose modification; and the reasons for dose modification within the population pharmacokinetic and exposure-response datasets. Provide the relevant descriptive statistics for each of these variables in support of the proposed dose in the Summary of Clinical Pharmacology.

**ARIAD’s Emailed Response of 4/14/16**: ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

19. Submit the following information and data to support the population pharmacokinetic analysis.

   a. SAS transport files (*.xpt) for all datasets used for model development and validation.
   b. Description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
   d. Model development decision tree or table which gives an overview of modeling steps.
   e. For the population analysis reports, submit the following.
      - Standard model diagnostic plots
      - Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
      - Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
      - Summary of the report describing the clinical application of modeling results.


**ARIAD’s Emailed Response of 4/14/16**: ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

20. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for brigatinib and its major active metabolites in the to-be-indicated patient population and include the results of this exploratory analysis in the NDA submission. Include an assessment of the effect of covariates on the exposure-response relationships. Refer to the FDA Guidance for Industry entitled “Exposure-Response Relationships –

ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

21. PBPK reports should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters of brigatinib, version of the software being used, simulation results, and conclusions. Provide the study report as PDF files (screenshots can be incorporated if required). Include the model files used to generate the final PBPK simulations. These files should be executable by the FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.

ARIAD’s Emailed Response of 4/14/16: ARIAD acknowledged FDA’s comment and stated ARIAD would address the comment in the NDA submission. No discussion occurred at the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

ARIAD and FDA reached the following agreements relating to the contents of a complete application:

- The content of a complete application was discussed. No late major components will be submitted. ARIAD plans to submit a minor component that includes updated stability data for the drug substance and drug product within 30 days of the submission of the final component of the rolling NDA submission, as agreed during the CMC-only pre-submission meeting held on March 2, 2016.

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

- It was concluded that a REMS is not necessary for FDA to file the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. ARIAD intends to submit a complete application and therefore, there are no agreements for late submission of application components.

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.

We refer to your amendment dated August 25, 2015, which contained your initial Pediatric Study Plan (iPSP) and to your amendment dated February 4, 2016, which contained an Agreed Initial Pediatric Study Plan (iPSP) submitted in response to our letter of November 13, 2015. We confirmed our agreement to your February 4, 2016, Agreed iPSP in our March 7, 2016, letter, wherein we also provided additional comments that must be incorporated in your Agreed iPSP intended for submission in the appropriate section of a marketing application.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf) and [Pregnancy and Lactation Labeling Final Rule](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf) 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.”

<table>
<thead>
<tr>
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<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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Corresponding names and titles of onsite contact:

<table>
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<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
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<tr>
<td>2.</td>
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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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item⁠¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>Data listings, by study</td>
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<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
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</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.

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

ATTACHMENTS AND HANDOUTS
  • None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH S HER
04/19/2016
Dear Mr. Birri:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AP26113, brigatinib.

We also refer to the meeting between representatives of your firm and the FDA on March 2, 2016. The purpose of the meeting is to discuss the Agency’s responses to your CMC questions.

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, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA CMC Only

Meeting Date and Time: March 2, 2016, 9:00-10:00 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 110935
Product Name: AP26113, brigatinib
Indication: For cancer patients with ALK (b) (4) EGF receptor mutations

Sponsor/Applicant Name: ARIAD Pharmaceuticals, Inc.

Meeting Recorder: Steven Kinsley

FDA ATTENDEES

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anamitro Banerjee, Ph.D.</td>
<td>Acting Branch Chief</td>
</tr>
<tr>
<td>Ray Frankewich, Ph.D.</td>
<td>Quality Reviewer</td>
</tr>
<tr>
<td>Joyce Crich</td>
<td>Team Lead</td>
</tr>
<tr>
<td>Okpo Eradiri, Ph.D.</td>
<td>Biopharmaceutics Lead (acting)</td>
</tr>
<tr>
<td>Banu Zolnik, Ph.D.</td>
<td>Biopharmaceutics Reviewer</td>
</tr>
<tr>
<td>Ying Zhang, Ph.D.</td>
<td>Process Reviewer</td>
</tr>
<tr>
<td>Alex Viehmann, Ph.D.</td>
<td>Quality Reviewer</td>
</tr>
<tr>
<td>Olen Stephens, Ph.D.</td>
<td>Quality Reviewer</td>
</tr>
<tr>
<td>Bogdan Kurtyka, Ph.D.</td>
<td>Quality Reviewer</td>
</tr>
<tr>
<td>Steven Kinsley, Ph.D.</td>
<td>Regulatory Business Process Manager</td>
</tr>
</tbody>
</table>

SPONSOR ATTENDEES

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chris Murray, Ph.D.</td>
<td>Vice President, Technical Operations</td>
</tr>
<tr>
<td>Gary Allmaier, Ph.D.</td>
<td>Senior Director, Analytical Development &amp; Quality Control</td>
</tr>
<tr>
<td>Manisha Shrivastava, Ph.D.</td>
<td>Senior Staff Scientist, Analytical Development</td>
</tr>
<tr>
<td>Dauntel Verwijs, Ph.D.</td>
<td>Staff Scientist, Drug Product Operations</td>
</tr>
<tr>
<td>James Tierney</td>
<td>Associate Director, Quality Control</td>
</tr>
<tr>
<td>Leonard Rozamus</td>
<td>Senior Director, Chemical and Process Development</td>
</tr>
<tr>
<td>Pradeep Sharma, Ph.D.</td>
<td>Director, Chemical and Process Development</td>
</tr>
<tr>
<td>Douglas Shorten</td>
<td>Director, Program and Alliance Management</td>
</tr>
</tbody>
</table>
1.0 BACKGROUND

Brigatinib is a novel, orally-active tyrosine kinase inhibitor (TKI). Primary targets are activated, mutant forms of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), which play important roles in non-small cell lung cancer (NSCLC) and other cancers. Brigatinib potently inhibits activated variants of ALK, such as echinoderm microtubule-associated protein (EML4)-ALK, and variants of ALK including the L1196M gatekeeper mutation. In addition, brigatinib potently inhibits activated variants of ROS kinase. Activating gene rearrangements in ROS have recently been identified as driver mutations in some patients with NSCLC. Finally, the spectrum of kinase inhibitory activity of brigatinib includes other targets potentially important in oncogenesis. In in vitro assays, brigatinib also inhibits the activity of focal adhesion kinase and checkpoint kinase 2. The overall clinical data show that brigatinib exhibits potent anticancer activity in locally advanced or metastatic ALK+ NSCLC patients.

As this particular meeting is CMC focused, the regulatory history provided herein comprises only relevant CMC amendments. ARIAD has submitted several CMC-related information amendments to the IND following the original submission on 28 June 2011 as summarized below.

- Sequence 0003 (25 July 2011): Response to CMC Deficiencies to the Original IND.
- Sequence 0005 (08 September 2011): Response to Original IND CMC Review Comments.
- Sequence 0009 (07 February 2012): Introduction of formulated brigatinib tablets, 30 mg for use in clinical trials. The 30 mg tablet formulation replaced which was presented in the original IND.
- Sequence 0040 (20 February 2013): Introduction of minor drug product formulation modifications. Magnesium stearate “Formulation-2”.
- Sequence 0052 (26 June 2013): Continued drug product manufacturing process improvements were reported as an introduction to “Formulation-3” for use in clinical trials. The optimized formulation brigatinib drug (Section 9.3.2.1).
- Sequence 0064 (16 October 2013): Introduction of as an alternate brigatinib drug substance manufacturer.
- Sequence 0127 (26 February 2015): Introduction of an optimized manufacturing process for brigatinib drug substance. The process improvements serve to provide increased control of impurities and solid-state properties including particle size and morphology. Optimized analytical procedures for drug substance and drug product as well as enhancements to the drug product container closure system were also introduced with this amendment.
• Sequence 0141 (15 May 2015): Addition of an alternative drug product manufacturing facility, Penn Pharma, located in Tredegar, Gwent, United Kingdom and the introduction of a further tablet strength of 90 mg.
• Sequence 0154 (25 June 2015): Protocol amendment to add 90 mg strength tablet.
• Sequence 0162 (04 August 2015): Request for a Type B (CMC-specific) Meeting to discuss proposed Regulatory Starting Materials, drug substance impurity specifications, pre-approval inspections, and drug product stability protocol design.
• Sequence 0168 (27 August 2015): Provision of Type B Meeting briefing materials in support of a formal meeting granted in response to the request submitted as Sequence 0162 and scheduled for 27 September 2015
• Sequence 0175 (06 October 2015): Written request for clarification on topics including the assignment of Regulatory Starting Materials and drug substance impurity specification limits. This written request was submitted in response to the FDA pre-meeting comments provided for the 27 September 2015 Type B Meeting.
• Sequence 0177 (12 October 2015): Request for a Type B (CMC-specific) Meeting to discuss the proposed commercial drug product dissolution procedure and in-process controls for drug product manufacturing.
• Sequence 0182 (04 November 2015): Provision of Type B Meeting briefing materials in support of a formal meeting granted in response to the request submitted as Sequence 0177 and scheduled for 07 December 2015.
• Sequence 0188 (24 November 2015): Following review of the written request clarification (Sequence 0175) the Agency requested that ARIAD identify specific questions via email correspondence on 19 November 2015 for which clarification was sought. Consequently, ARIAD revised and truncated the original written response to request feedback specifically on the additional information provided pertaining to the assignment of Regulatory Starting Materials and drug substance impurity specification limits.

The purpose of this Pre-NDA CMC-specific meeting is to present an overview of the content plan for submission of specific Module 2 and 3 components, including a summary of stability data to be submitted at the initiation of the NDA and stability data that may be provided at the final stages of the rolling submission. In addition, ARIAD is seeking advice related to CMC aspects of the brigatinib program including, but not limited to, the proposed commercial dissolution procedure, proposed drug product specifications, the proposed shelf life for

FDA sent Preliminary Comments to ARIAD Pharmaceuticals on February 24, 2016.

2.0 DISCUSSION

Question 1.
ARIAD has performed extensive dissolution method development studies utilizing multiple approaches to experimental design in order to define and optimize dissolution operating conditions which effectively satisfy all target method attributes. In particular, an agitation rate of 70 rpm has been selected to excipients while maintaining adequate method sensitivity and robustness.

Does the Agency agree that the proposed agitation rate of 70 rpm is sufficiently justified as a target operating parameter for the brigatinib commercial dissolution procedure?
**FDA Response to Question 1:**

No, FDA does not agree. Based on the data provided in the meeting briefing document, it appears that similar drug release profiles were obtained at agitation speed. Furthermore, it is noted that dissolution data are normalized based on the drug concentration data at the minute time point. This approach is not acceptable; provide drug release data based on the label claim in the NDA. Additionally, provide comparative dissolution profiles of batches manufactured at Penn Pharma sites. Overall assessment of the adequacy of the dissolution method will be made during the NDA review based on the totality of the dissolution data, including the discriminating ability of the method.

**Discussion:** Ariad stated that the proposed agitation speed of 70 rpm does not provide adequate robustness to the method. FDA stated that Ariad’s rationale for using 70 rpm seems acceptable (see Section 6.0, Attachments and Handouts). There was agreement that justification for the use of 70 rpm agitation speed will be included in the NDA submission. Ariad agreed to report dissolution data on the basis of the label claim in the NDA.

**Question 2.**

The proposed commercial dissolution procedure for release and stability testing of brigatinib tablets, 30 mg and 90 mg is performed according to the current USP General Chapter <711>, using USP Apparatus II (paddles). The corresponding proposed commercial dissolution acceptance criterion has been selected in accordance with ICH Q6A, Decision Tree # 7. The criterion is based on a thorough statistical analysis of the dissolution profiles from release and stability data sets or pivotal clinical and registration drug product lots.

Does the agency agree with the approach to the development of a commercial dissolution specification for brigatinib tablets, 30 mg and 90 mg?

**FDA Response to question 2:**

Yes, the approach taken to arrive at the proposed dissolution acceptance criterion appears reasonable. However, acceptability of the proposed dissolution acceptance criterion for Ariad’s product will be made during NDA review based on the totality of the provided dissolution data.

**Discussion:** No discussion.

**Question 3.**

Ariad intends to register brigatinib drug product as 30 mg and 90 mg dose strengths in the New Drug Application (NDA). Both strengths manufactured. The expected amount of stability data at the start of the rolling submission and at the end of the NDA process are summarized in Table 3. Based on the proposed provision of drug product stability data, Ariad intends to propose a shelf life of 24 months for brigatinib tablets, 30 mg and 90 mg.

Does the Agency agree that the proposed provision of stability data is sufficient to justify a shelf-life of 24 months for brigatinib tablets, 30 mg provided that the data indicate little to no change over time?
FDA Response to question 3:
As per the PDUFA V agreement, a complete application is expected at time of submission, which includes 12 months of stability data. Stability updates may be provided via amendment to the NDA within 30 days of submission. Therefore, it is acceptable to file the NDA with 6-months of stability data for both strengths and then provide an amendment within 30 days of NDA submission to provide the 12-month stability data. Additional stability amendments provided after this time period will be reviewed as resources allow. The proposed stability package would meet these requirements for the 30-mg tablet manufactured at [REDACTED] ability to bridge the stability data [REDACTED] to the batches manufactured at Penn Pharma will be determined at the time of NDA review.

Additionally, since the 90 mg strength is the highest proposed strength, the stability data from the 30 mg strength cannot be used to bracket the 90 mg strength. The shelf-life of the 90-mg strength will be determined on the basis of the available stability data for that strength independent of the determination for the 30-mg strength.

Extrapolation of the data for both strengths is possible depending on the quality of the data. A shelf life will be granted based on the data reviewed for both strengths at the time of NDA action date.

Discussion: There was no discussion of the response to question 3.

Question 4.
In an effort to ensure continuous product supply, brigatinib drug substance manufacturing process has been formally transferred to an additional manufacturing facility. [REDACTED] The process design, control strategy, test methods, and specifications at [REDACTED] ARIAD intends to register both drug substance manufacturers as commercial facilities in the original NDA. For ease of review, an overview of the brigatinib drug substance manufacturing history at [REDACTED] is presented in Table 1.

Does the Agency agree with the proposed approach for the successful inclusion of [REDACTED] as an additional drug substance manufacturer in the brigatinib NDA?

FDA Response to question 4:
There is insufficient information in Ariad’s meeting package to answer question 4. No specifics regarding the process used at [REDACTED] are provided other than Ariad’s statement that the process design, control strategy, test methods, and specifications are essentially the same.

Provide a comparison between the processes used by [REDACTED] to produce brigatinib drug substance. Starting materials, intermediates, basic chemistry, and impurity profile of the processes should be the same. Differences in these aspects of the processes should be explained and it should be demonstrated why the drug substance can be considered equivalent despite the differences. Differences in other aspects of the processes under comparison (e.g. solvents) should be briefly summarized.
**Additional Comments Question 4:** To follow up on Ariad’s response dated November 24, 2015 regarding the proposed acceptance criterion of \( \text{impurity } \) % for impurity \( \text{impurity } \): perform a bridging study comparing the response of \( \text{response } \) in HPLC Method 4 to the equivalent response in Method 2, and determine a scale factor for results of the two procedures. Results should demonstrate that Method 4 is more sensitive (or the same) with respect to Method 2. Also results should allow estimation of the level of \( \text{level } \) in Batch 10-145-57-17 at the time it was used in toxicology studies as measured by Method 4. This data will support (or not) the proposed acceptance criterion for \( \text{criterion } \).

**Discussion:** Ariad will provide the requested information for \( \text{information } \). The FDA has no concerns on the facility at this time, but will need a side-by-side comparison of the processes at \( \text{processes } \) in the NDA submission. Ariad will provide data on registration batches from both facilities in their NDA submission.

FDA clarified the additional comment that a bridging study must be performed to show that Method 4 is more sensitive or equivalent to Method 2 regarding impurity \( \text{impurity } \). Ariad stated they will do the study to compare Method 2 to Method 4.

**Question 5.**
ARIAD intends to utilize \( \text{utilize } \) analysis as an alternative \( \text{alternative } \) at Penn Pharmaceutical Services Ltd. (Penn), one of two proposed drug product manufacturing sites. The corresponding sampling plan and acceptance criteria have been developed in accordance with \( \text{developed } \).

Does the Agency agree with the proposed implementation strategy for sampling and acceptance criteria for heightened stratified dosage unit analysis to be performed at Penn?

**FDA Response to question 5:**
The Agency agrees with the proposed two-stage sampling plan and acceptance criteria that has been developed in accordance with \( \text{developed } \).

It is not clear whether you plan to implement a three-stage plan. In the NDA submission, clarify when you will move to stage 3, as well as the sample size and acceptance criteria of stage 3.

**Discussion:** There was no discussion of the response to question 5.

**Question 6.**
Ariad intends to provide an overview of the strategy for submission of a complete New Drug Application (NDA) within the pre-NDA briefing materials, specifically, as it pertains to Module 3 and the Quality Overall Summaries (QOS).

Does the agency agree that the overall approach for submission of Module 3 and Module 2.3 QOS content is appropriate for the brigatimib New Drug Application?
**FDA Response to question 6:**

The proposal to submit the NDA with separate drug substance and drug product sections based on the different manufacturing sites is acceptable. Inclusion of cross references to the corresponding sections is also acceptable, provided there are no differences in the cross referenced sections. Additionally, in Module 2, provide side-by-side summaries of the differences for corresponding sections.

**Additional Comments Question 6:**

Question #6 in the meeting package has the following statement, “Finally, a summary of established conditions shall be presented using a tabular format with the drug substance QOS, 2.3.S and the drug product QOS, 2.3.P.” Because ICH Q12 has not been finalized and the topic of “established conditions” is still under negotiation, FDA recommends Ariad schedule a separate meeting to discuss this topic prior to the NDA submission. This discussion should include proposals for established conditions, supportive data, justification for the claims, and a high level discussion of how lifecycle management will be handled with established conditions claims. Submitting established conditions claims in the NDA without prior discussion could require significant negotiation during the review clock, which could impact the ability of the review team to complete their review.

**Discussion:** Ariad will provide side-by-side comparisons of the drug substance and drug product facilities in Module 3 of the NDA submission. FDA asked if any comparability issues are anticipated; Ariad responded not at this time.

### 3.0 General Comments

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 on the follow page 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.”
4.0 ISSUES REQUIRING FURTHER DISCUSSION:

In the development and expected production of AP26113, brigatinib, Ariad has used two different sites for the API and two different sites for the production of the drug product. It is not clear which facilities have been involved in production of the registration batches and/or how the data will be bridged from one site to another. FDA requests that Ariad provides a written response as an amendment to the IND which clearly indicates sources (API and Drug Product) for all registration batches, preferably as a table.

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

<table>
<thead>
<tr>
<th>Action Item/Description</th>
<th>Owner</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide an Amendment to the IND containing clear description of sources (combination of API and Drug Product) used in the production of material for the Registration Batches.</td>
<td>Ariad</td>
<td>Prior to the Pre-NDA meeting scheduled for April 15, 2016</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
STEVEN A KINSLEY
03/08/2016

ANAMITRO BANERJEE
03/08/2016
Dear Mr. Slugg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Brigatinib (AP26113).”

We also refer to the June 30, 2015, Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting between representatives of your firm and the FDA to discuss ARIAD’s drug development program for brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib.

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, please call me at (301) 796-5890.

Sincerely,

{Tina Ennis, M.S.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research}

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting

Meeting Date and Time: Tuesday, June 30, 2015, 11:00 AM-12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: 110935
Product Name: Brigatinib
Indication: Treatment of patients with anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib.

Sponsor/Applicant Name: ARIAD Pharmaceuticals, Inc.

Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Tina Ennis, M.S.

FDA ATTENDEES
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Oncology Products 2
Patricia Keegan, M.D. Division Director
Gideon Blumenthal, M.D. Medical Officer Team Lead
Dickran Kazandjian, M.D. Medical Officer
Okpo Eradiri, Ph.D. Acting Biopharmaceutics Lead
Whitney Helms, Ph.D. Pharmacology/Toxicology Team Lead
Liang Zhou, Ph.D. Chemistry, Control and Manufacturing Reviewer
Jeanne Fourie Zirkelbach, Ph.D. Clinical Pharmacology Team Lead
Elimika Pfuma Fletcher, Pharm.D., Ph.D. Clinical Pharmacology/Genomics Reviewer
Janet Jiang, Ph.D. Statistical Reviewer
Melanie Pierce, M.S. Chief Project Management Staff (Acting)
Tina Ennis, M.S. Regulatory Project Manager

ARIAD Pharmaceuticals, Inc.
Daniel Bollag, Ph.D. Senior Vice President, Regulatory Affairs and Quality
Timothy Clackson, Ph.D. President, Research and Development and Chief Scientific Officer
Maureen Conlan, M.D. Senior Medical Director, Clinical Research and Development
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 30, 2015, between ARIAD and the Division of Oncology Products 2. 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.


BACKGROUND

Regulatory:
On March 13, 2015, ARIAD Pharmaceuticals, Inc. (ARIAD) submitted a meeting request (SDN 131) for an Initial Multidisciplinary meeting as requested in FDA’s October 1, 2014, letter. The purpose of the meeting is to discuss ARIAD’s drug development program for brigatinib for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib. The pre-meeting briefing document was received on June 1, 2015, as SDN 148.
ARIAD would like to obtain feedback on the ability of the development program to support a New Drug Application (NDA) and to obtain preliminary advice on the contents of the planned NDA. Under this development program, ARIAD will seek accelerated approval of brigatinib based on the demonstration of durable objective response rates observed in the Study AP26113-13-201 (ALTA), supported by anti-tumor activity observed in Study AP26113-11-101, for the following proposed indication:

For the treatment for patients with metastatic ALK-positive NSCLC who have crizotinib.

ARIAD will conduct a single confirmatory trial to verify clinical benefit of brigatinib and expects that trial will be initiated by early 2016. The proposed confirmatory trial is a randomized, multicenter study to be conducted in patients with advanced ALK-positive NSCLC who have not previously received ALK-directed therapy and is intended to support the following proposed indication:

For the treatment of patients with metastatic anaplastic lymphoma kinase positive (ALK-positive) non-small cell lung cancer (NSCLC) who have.

On March 24, 2011, a preIND meeting was held to discuss submission of an IND for AP26113 (brigatinib) for the treatment of patients with cancers containing ALK-rearrangements or EGFR mutations.

On June 28, 2011, ARIAD submitted IND 110935; the IND was allowed to proceed on July 26, 2011.

On March 18, 2013, a meeting was held with ARIAD to discuss the design of a proposed multicenter, single-arm trial of brigatinib to be conducted in patients with locally advanced or metastatic NSCLC with ALK rearrangements who have experienced failure of crizotinib therapy after at least one prior chemotherapy regimen at the “to-be determined” recommended Phase 2 dose and to discuss the adequacy of the planned non-clinical and clinical pharmacology assessment of brigatinib. FDA agreed that the completed and planned pharmacology, safety pharmacology, and toxicology studies to support the proposed NDA seeking accelerated approval appeared sufficient to support an NDA filing for the proposed indication but that additional nonclinical studies may be needed to support a marketing application for a different indication. FDA stated that the planned clinical pharmacology studies were not sufficient to support a future NDA; specifically a bioavailability and food effect study would be required. In addition, the QT plan would need to be evaluated based upon available data for its adequacy and to determine if additional QT assessments would be needed. With regard to the proposed clinical study, FDA stated that a single arm trial of sufficient size to provide reasonable estimates of the treatment effect that demonstrates a clinically important response rate and prolonged duration of response in crizotinib resistant patients may be adequate to support a request for accelerated approval provided that the benefit-risk assessment was also favorable. FDA further stated that the ORR as determined by independent review using RECIST version 1.1 is acceptable as the
primary analysis, however analysis of time-to-event endpoints of progression-free and overall survival and of quality of life would not be interpretable in a single arm trial.

A meeting to discuss the design of the proposed confirmatory trial was scheduled for October 24, 2013. The meeting was cancelled by ARIAD upon receipt of FDA’s preliminary responses.

On October 1, 2014, ARIAD was granted Breakthrough Therapy Designation for brigatinib for the “treatment of patients with anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib.”

**Chemistry, Manufacturing, and Control:**
Two strengths of the film-coated tablets have been formulated for brigatinib, in 30 mg and 90 mg. The 30 mg tablets are: round, white film-coated tablets, debossed “U3” on one side and plain on the other side. The 90 mg tablets are: oval, white film-coated tablets, debossed “U7” on one side and plain on the other side. Both strengths are currently packaged in HDPE bottles *the 30 mg film-coated tablet.*

**Non-Clinical:**
ARIAD states that they have conducted nonclinical safety and toxicity studies in mice and rats, ADME studies, 28-day general toxicology studies in rats and Cynomolgus monkeys, in vitro and in vivo genotoxicity studies, and a phototoxicity study in rats. Assessments of cardiovascular, pulmonary, CNS, and renal safety are also ongoing or completed and six month GLP-compliant toxicology studies in rats and monkeys are underway. ARIAD plans to conduct an embryofetal development toxicology in rats. If results of the rat study are negative, then ARIAD will conduct an embryofetal development study in rabbits as well.

Dose-dependent increases in mortality occurred at single brigatinib doses of ≥125 mg/kg in mice and at single brigatinib doses of ≥250 mg/kg in rats. In the 28-day GLP oral toxicology/toxicokinetics study in rats, oral administration of brigatinib at doses of 30 or 60 mg/kg/day resulted in a dose-dependent increase in mortality at 30 and 60 mg/kg/day, which led to the cessation of dosing in the 60 mg/kg/day dose group toward the end of Week 1. A clear spectrum of clinical signs of toxicity preceded the deaths of the animals. The key histopathological findings in rats at the 30 and 60 mg/kg/day dose levels that died prematurely and in some 30 mg/kg/day rats that survived the 28-day treatment period were hematopoietic hypopcellularity in the bone marrow, and lymphoid depletion in the spleen, thymus and other lymphoid tissues. ARIAD states that other notable gross anatomic or microscopic findings, including bone and gastrointestinal (GI) pathologies, attributable to brigatinib were seen primarily in rats that died prematurely.

In the 28-day GLP monkey oral toxicology/toxicokinetic study, clinical signs of toxicity, moribundity, and mortality were evident beginning on Day 3 after daily oral administration of 45 mg/kg/day brigatinib. Consequently, dosing of all animals in the 45 mg/kg/day dose group was stopped on Day 7 or 8. The cause of premature death was attributed to brigatinib related GI toxicity, which involved all segments of the GI tract, but was most severe in the stomach and small intestines. Other prominent histopathological findings in monkeys that died prematurely
and in animals treated with 15 and 45 mg/kg/day brigatinib that survived to the terminal sacrifice on Day 30 were generally similar to those seen in rats, including lymphoid atrophy/necrosis and bone marrow hypocellularity. ARIAD states that no changes attributable to brigatinib were seen at terminal sacrifice in the 7.5 mg/kg/day treatment group, or in any dose group at the end of the 28-day recovery period.

No evidence of cutaneous phototoxicity or ocular phototoxicity was observed in rats after a single oral administration of brigatinib at doses up to 60 mg/kg.

ARIAD states that there was no evidence of genotoxicity observed in a bacterial reverse mutation assay or in a chromosomal aberration test in human peripheral blood lymphocytes performed with brigatinib.

**Clinical Pharmacology:**
The proposed studies intended to characterize the pharmacokinetics (PK) of brigatinib in the proposed NDA are summarized in the table below. In addition, ARIAD plans to collect sparse PK samples in the ALTA trial. Based on the third amendment to the ALTA trial, submitted June 25, 2015, ARIAD will switch from the 30 mg tablet, Formulation-3, to the 90 mg tablet. Data bridging from the 30 and 90 mg tablet strength of Formulation-3 will include sparse PK data and in vitro dissolution profile data.

ARIAD submitted QT data from to the IND on May 18, 2015, and stated that they do not plan to perform a dedicated or thorough QT trial.
**Completed and Planned Clinical Pharmacology Trials**

<table>
<thead>
<tr>
<th>Trial# and Status</th>
<th>N</th>
<th>Trial Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP26113-13-102</td>
<td>48</td>
<td>PK in Japanese versus Caucasians: Single doses of 90, 120 or 180 mg in 24 Japanese-positive 24 Caucasian subjects</td>
</tr>
<tr>
<td>AP26113-13-103</td>
<td>8</td>
<td>Preliminary Food Effect: Single 180 mg dose fasted (Day 1) or fed (Day 10)</td>
</tr>
<tr>
<td>AP26113-13-104</td>
<td>6</td>
<td>ADME Trial: Single 180 mg dose of [¹⁴C] Brigatinib given as a solution</td>
</tr>
</tbody>
</table>
| AP26113-15-105  | 60  | DDI Trial: Three-Part, Open-Label, One Sequence Crossover Trial:  
• Itraconazole: 90 mg brigatinib alone on Day 1, itraconazole 200 mg BID on Days 17-25, 90 mg brigatinib co-administered on Day 21.  
• Gemfibrozil: 90 mg brigatinib alone on Day 1, gemfibrozil 600 mg BID on Days 17-25, 90 mg brigatinib co-administered on Day 21.  
• Rifampin: 180 mg brigatinib alone on Day 1, rifampin 600 mg QD on Days 17-25, 180 mg brigatinib co-administered on Day 22. |
| Planned          | TBD | Hepatic Impairment: Single dose of 90 or 180 mg brigatinib in volunteers with hepatic impairment (groups not stated) and matched healthy volunteers |
| Planned          | TBD | Renal Impairment: Single dose of 90 or 180 mg brigatinib in volunteers with renal impairment (groups not stated) and matched healthy volunteers |
| Planned          | TBD | Pivotal Food Effect: Single 180 mg dose fasted (Day 1) or fed (Day 17) |

**Clinical:**

*AP26113-11-101 (“101”, NCT01449461)*

Protocol AP26113-11-101 was the IND-enabling trial. The original protocol was submitted on June 28, 2011, and has been amended six times. This is a first-in-human, open-label, multi-center, dose-escalation (“3 plus3” design) and multi-cohort, activity-estimating trial. The first portion of the study was designed to evaluate the safety, tolerability, PK, and determine the recommended Phase 2 dose (RP2D) in 30-70 patients with various cancers (except leukemia) and no effective alternative therapy. Following determination of the RP2D, approximately 20 patients were to be enrolled in cohorts 1, 3, and 4. Cohort 5 enrolled 25 patients, and 50 patients in cohort 2. Each of the following histologically and molecularly defined cohorts:

1. Patients with ALK-positive NSCLC who have not received ALK-targeted therapy (ALK-therapy naive) patients who are naive to ALK-targeted therapies (cohort 1).
2. Patients with ALK-positive NSCLC with resistance to ALK-targeted therapy (cohort 2).
3. Patients with NSCLC bearing activating EGFR mutations with resistance to a prior EGFR inhibitor (cohort 3).
4. Patients with any cancer containing abnormalities in ALK, EGFR, ROS1, or other targets against which brigatinib is active (cohort 4).

5. Patients with ALK-positive NSCLC and active brain metastases, regardless prior treatment with crizotinib (cohort 5).

The objectives of this study are to determine the safety profile, including identification of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs), determine the recommended phase 2 dose (RP2D), examine the pharmacokinetic profile, describe preliminary antitumor activity in ALK-positive or EGFR mutation-positive (EGFRm) NSCLC, and perform exploratory analyses including molecular assessments. The primary endpoint of the expansion cohorts 1-4 is the overall response rate (using RECIST). The primary endpoint of expansion cohort 5 is the CNS response rate (using RECIST). There was no justification for the proposed sample sizes for the expansion cohort and all analyses are descriptive only.

Results
The study is being conducted in nine centers in the United States and Spain. Enrollment is completed with 137 patients enrolled, however investigational drug administration and follow-up for study endpoints is ongoing. The distribution of patients by dose level is summarized in the following figure. The distribution of patients enrolled in the second portion (expansion) of the trial is not provided in the pre-meeting briefing document, however based on Protocol Amendment #6, expansion cohorts 3 and 4 were closed prior to fully enrolling.

ARIAD states that the dosing regimen of brigatinib 180 mg orally, once daily (QD), was chosen as the RP2D and the treatment regimen to be administered in the second portion of the study in the five expansion cohorts listed above. However, the dosing regimen was modified based on the 14% incidence of serious early onset pulmonary events (dyspnea, hypoxia, pneumonia, and ground glass and interstitial chest CT findings) at this dose level. The study was modified to further explore the tolerability and anti-tumor activity of two additional dosage regimens: (1) brigatinib 90 mg QD and (2) brigatinib 90 mg QD for the first 7 days followed by brigatinib 180 mg QD.
The safety experience is based on data obtained in 137 patients who received brigatinib, of whom 65 (47%) are still receiving brigatinib. The safety data are based on a median duration of exposure of 165 days (5.4 months) and a data cut-off date of August 4, 2014. Across all dose levels, 97% (133/137) of the patients experienced at least one treatment-emergent adverse event (TEAE) and 41% (56/137) experienced at least one serious treatment emergent adverse event (SAE). Sixty-two patients (45.3%) have experienced at least 1 TEAE leading to a dose delay or reduction, or discontinuation from the study. Of 137 patients treated, the mean dose intensity was 142 mg/day. A summary of the overall incidence of adverse events by dose level (or a combination of two dose levels) are summarized in the table below, abstracted from the briefing document.

### Table 23: Patient Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=137</th>
<th>History of ALK+ NSCLC N=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>57 (29-83)</td>
<td>54 (29-83)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>79 (58)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>110 (80)</td>
<td>65 (82)</td>
</tr>
<tr>
<td>Asian</td>
<td>17 (12)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (7)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>128 (93)</td>
<td>79 (100)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>119 (87)</td>
<td>74 (94)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (7)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Prior crizotinib</td>
<td>76 (55)</td>
<td>71 (90)</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 regimen</td>
<td>36 (26)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>2 regimens</td>
<td>34 (25)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>≥3 regimens</td>
<td>31 (23)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42 (31)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>1</td>
<td>92 (67)</td>
<td>48 (61)</td>
</tr>
<tr>
<td>2</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

### Table 24: Patient Disposition and Treatment Exposure

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=137</th>
<th>History of ALK+ N=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remain on study, n (%)</td>
<td>65 (47)</td>
<td>56 (71)</td>
</tr>
<tr>
<td>Discontinued treatment, n (%)</td>
<td>72 (53)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Documented progressive disease</td>
<td>42 (31)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>13 (10)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Clinical progressive disease</td>
<td>7 (5)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>3 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>
ARIAD states that treatment-emergent adverse events of Grade 3 or greater occurring in ≥2% of patients across the all dose levels were: lipase increased (6.6%), dyspnea (5.8%), hypoxia (4.4%), neoplasm progression (4.4%), amylase increased (3.6%), fatigue (3.6%), pneumonia (3.6%), hypertension (2.9%), pulmonary embolism (2.9%), ALT increased (2.2%), hyponatremia (2.2%).

Serious adverse events, regardless of causality occurring in ≥2% of patients across all dose levels were: dyspnea (7%), pneumonia (5%), hypoxia (4%), neoplasm progression (4%), pyrexia (2%), and pulmonary embolism (2%). There were 13 (10%) patients across all dose levels who discontinued treatment for adverse events; one patient each had brigatinib discontinued for the following adverse events: increased amylase, acute renal failure, pneumonitis, muscle spasms, rash maculo-papular, gastric ulcer hemorrhage, tachycardia, dyspnea and suicidal ideation. In addition, four patients discontinued brigatinib for multiple concurrent adverse events:

- pneumonia, pulmonary embolism and pleural effusion (n=1)
- dyspnea, hypoxia and hypotension (n=1)
- dyspnea and hypoxia (n=2)

Across the study population, the major safety signal identified was early onset pulmonary symptoms (defined as within first 7 days of treatment) which occurred in 10% of the patients (13/137). Based on information provided in the pre-meeting package, early onset pulmonary symptoms were the dose-limiting toxicity and defined the maximum tolerated dose occurring as follows across dose levels:

### Table 26: Treatment-Emergent Adverse Events by Dose Cohort ≥ 10% Overall, All Grades

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>30, 60 mg</th>
<th>90 mg</th>
<th>120 mg</th>
<th>90 mg</th>
<th>180 mg</th>
<th>180 mg</th>
<th>240, 300 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=6²</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (50)</td>
<td>0 (28)</td>
<td>6 (44)</td>
<td>10 (31)</td>
<td>26 (54)</td>
<td>8 (53)</td>
<td>61 (45)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (17)</td>
<td>5 (28)</td>
<td>8 (44)</td>
<td>13 (41)</td>
<td>15 (31)</td>
<td>8 (53)</td>
<td>50 (37)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (33)</td>
<td>4 (22)</td>
<td>7 (39)</td>
<td>12 (38)</td>
<td>13 (27)</td>
<td>12 (80)</td>
<td>50 (37)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1 (17)</td>
<td>5 (28)</td>
<td>6 (33)</td>
<td>8 (25)</td>
<td>8 (17)</td>
<td>8 (53)</td>
<td>36 (26)</td>
<td></td>
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<tr>
<td>Headache</td>
<td>0</td>
<td>5 (28)</td>
<td>6 (33)</td>
<td>7 (22)</td>
<td>11 (23)</td>
<td>6 (40)</td>
<td>35 (26)</td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td>0</td>
<td>3 (17)</td>
<td>7 (39)</td>
<td>5 (16)</td>
<td>8 (17)</td>
<td>6 (40)</td>
<td>29 (21)</td>
<td></td>
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<tr>
<td>Amylase increased</td>
<td>0</td>
<td>5 (28)</td>
<td>4 (22)</td>
<td>8 (25)</td>
<td>7 (15)</td>
<td>3 (20)</td>
<td>27 (20)</td>
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<tr>
<td>Vomiting</td>
<td>1 (17)</td>
<td>1 (6)</td>
<td>5 (28)</td>
<td>3 (9)</td>
<td>12 (25)</td>
<td>5 (33)</td>
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<td>AST increased</td>
<td>0</td>
<td>2 (11)</td>
<td>6 (33)</td>
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<td>2 (13)</td>
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<td>Lipase increased</td>
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<td>4 (22)</td>
<td>4 (22)</td>
<td>8 (25)</td>
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<tr>
<td>Constipation</td>
<td>1 (17)</td>
<td>2 (11)</td>
<td>5 (28)</td>
<td>4 (13)</td>
<td>4 (8)</td>
<td>5 (33)</td>
<td>21 (15)</td>
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<tr>
<td>Decreased appetite</td>
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<td>3 (17)</td>
<td>1 (6)</td>
<td>2 (6)</td>
<td>9 (19)</td>
<td>5 (33)</td>
<td>20 (15)</td>
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<tr>
<td>Muscle spasms</td>
<td>1 (17)</td>
<td>1 (6)</td>
<td>2 (11)</td>
<td>3 (9)</td>
<td>9 (19)</td>
<td>3 (20)</td>
<td>19 (14)</td>
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<tr>
<td>Pyrexia</td>
<td>0</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>4 (13)</td>
<td>6 (13)</td>
<td>3 (20)</td>
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<td>5 (16)</td>
<td>4 (8)</td>
<td>1 (7)</td>
<td>15 (11)</td>
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<tr>
<td>Arthralgia</td>
<td>1 (17)</td>
<td>3 (17)</td>
<td>0</td>
<td>6 (19)</td>
<td>5 (10)</td>
<td>0</td>
<td>15 (11)</td>
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<tr>
<td>Back Pain</td>
<td>1 (17)</td>
<td>1 (6)</td>
<td>3 (17)</td>
<td>4 (13)</td>
<td>5 (10)</td>
<td>1 (7)</td>
<td>15 (11)</td>
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<tr>
<td>Hypertension</td>
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<td>0</td>
<td>3 (17)</td>
<td>5 (16)</td>
<td>6 (13)</td>
<td>1 (7)</td>
<td>15 (11)</td>
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<tr>
<td>Peripheral edema</td>
<td>1 (17)</td>
<td>1 (6)</td>
<td>3 (17)</td>
<td>2 (6)</td>
<td>3 (6)</td>
<td>5 (33)</td>
<td>15 (11)</td>
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</tbody>
</table>
- 100% (2/2) patients at 300 mg QD dose level
- 20% (2/10) patients at the 240 mg QD level
- 14% (6/44) patients at the 180 mg QD level,
- 9% (1/11) patients at the 120 mg QD level, and
- 11% (2/18) patients at 90 mg QD dose level

ARIAD states that the addition of a 90-mg QD 7-day lead-in to therapy with 180 mg QD appeared to lessen the incidence of early pulmonary symptoms, in that none of the 32 patients who received brigatinib at 90 mg for 7 days than 180 mg QD thereafter experienced early onset pulmonary symptoms within the first 7 days at 90 mg or after escalation to 180 mg.

Additional adverse events which may be dose-related are nausea, diarrhea, fatigue, decreased appetite, muscle spasms, pyrexia, and peripheral edema.

ARIAD states that across all dose levels and phases of the study, there were 72 patients with ALK-positive NSCLC who were evaluable for response among the 79 patients (71 patients with prior crizotinib treatment and 8 patients who had not received prior crizotinib) with ALK-positive NSCLC enrolled in the study. The criteria for “evaluable for response” is not specified in the pre-meeting briefing document. A summary of the anti-tumor activity abstracted from the briefing document based on “evaluable patients” is summarized in the table below.

<table>
<thead>
<tr>
<th>Response Outcome</th>
<th>ALK-positive NSCLC; prior crizotinib (n=65)</th>
<th>ALK-positive NSCLC; crizotinib naïve (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>48% (31/65)</td>
<td>86% (6/7)</td>
</tr>
<tr>
<td>Range for duration of responses (months)</td>
<td>Not provided</td>
<td>3.7+ to 18.5+</td>
</tr>
<tr>
<td>Unconfirmed ORR</td>
<td>69% (45/65)</td>
<td>100%</td>
</tr>
<tr>
<td>Duration of response (unconfirmed ORR)</td>
<td>Not provided</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

**AP26113-13-201 (“ALTA”, NCT02094573)**
Protocol AP26113-13-201 (ALTA) was submitted on August 6, 2013, and has been amended three times. The first amendment to the protocol, submitted February 14, 2014, added a second treatment arm and, as currently designed, this is a randomized, two-dose, two-arm, multicenter, international study evaluating the antitumor activity of brigatinib in patients with ALK-positive NSCLC with disease progression following treatment with crizotinib. Patients will be randomized (1:1) to receive:

- Arm A1: brigatinib 90 mg orally, once daily or
- Arm B: brigatinib 90 mg orally, once daily for 7 days, then brigatinib 180 mg QD.

Treatment will continue until disease progression or intolerable toxicity. Treatment may be continued after progression, at the discretion of the investigator. On Arm A1, at the time of
progression, the patient may continue at the same dose or the patient’s dose may be escalated from 90 mg QD to 180 mg QD. For patients on either arm receiving 180 mg QD, at the time of progression, treatment may continue if there is still evidence of “clinical benefit.”

The key eligibility criteria are histologically or cytologically confirmed, locally advanced or metastatic, NSCLC with documented ALK rearrangement by a positive result from the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or documented ALK positivity by a different test and tissue available for the Vysis® FISH test. Patients are required to have experienced progressive disease while on crizotinib.

The primary endpoint is confirmed objective response rate as assessed by the investigator according to RECIST v1.1. The study sample size of at least 109 patients in each arm will allow the study to have an approximate 90% power to rule out an uninteresting rate of 20% when the true rate is 35% or higher with alpha=0.025 two-sided. All patients who are randomized will be included in the primary analysis of efficacy. All patients who receive at least 1 dose of AP26113 will be included in the analysis of safety. Each dosing regimen will be summarized separately. No inferential comparisons between the two regimens will be performed. For the primary efficacy test of the primary endpoint, ORR as assessed by the investigator, the overall alpha of 0.05 two-sided will be split in half to adjust for the fact that a test of each regimen treatment group will be performed. For each dosage regimen, the primary analysis of the primary endpoint will be performed using a 2-sided exact 97.5% confidence interval. The primary analysis is planned to be conducted when all ongoing patients have completed their Cycle 6 disease assessment.

Results
The study is being conducted at approximately 100 study centers in 18 countries in North America, Europe, Asia and Australia. The first patient was randomized in June 2014; as of April 30, 2015, 119 of the planned 218 patients have been enrolled across 69 study sites. No preliminary data are provided on efficacy or safety in the pre-meeting briefing document.

Planned Confirmatory Trial
ARIAD proposes to conduct a randomized, multicenter study will be conducted in patients with metastatic, ALK-positive NSCLC
**Proposed Plan for Interactions with FDA Regarding the Original NDA**

ARIAD plans on requesting a rolling NDA submission with the CMC and Nonclinical modules preceding the submission of the Clinical module.

<table>
<thead>
<tr>
<th>Estimated timing relative to final component of rolling NDA submission</th>
<th>Milestones</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Original NDA Submission                                               | Final Rolling Submission, completing the Original NDA Submission | Module 1
  • Draft Prescribing Information  
  • Priority Review Request  
  • Administrative information relying on Clinical Data |
| +3 months                                                              | Amendment: Updated Components as described under PDUFA V  
  • Safety Update Report | Module 1
  • Updated Draft Prescribing Information (as needed) |
|                                                                      | Module 2
  • Addendum to 2.5 Clinical Overview (as needed)  
  • Addendum to 2.7 X Clinical Summaries (as needed) |
|                                                                      | Module 3
  • Updated 3.2.5.8.3 Stability Data for:  
    • 9 months 30 mg  
    • 9 months 90 mg  
  • Updated 3.2 P.8.3 Stability Data for:  
    • Penn Pharma |
|                                                                      | Module 5
  • Updated efficacy (duration of response) & updated safety data from ALTA, in compliance with 21 CFR 314.50(d)(5)(vi) |

*This NDA submission plan is based on the projected recriment from the ALTA study and other planned studies and may be subject to change*

The rolling submission of clinical data will include complete Module 2 clinical sections (2.5 Clinical Overview and 2.7 Clinical Summaries) as well as clinical study reports from 101 and ALTA. Initial submission of safety and efficacy data from ALTA will include a minimum of 16 weeks follow up from all ongoing patients. Using current enrollment and projected accrual rates, the estimated median follow up in the initial submission of data from ALTA to be approximately 8 months, with an estimated maximum of 22 months follow up. Ariad purports that a minimum
of 16 weeks follow up would provide a conservative estimate of response yet include a significant majority of confirmed responses that will be observed on trial.

A safety and efficacy amendment is planned that is intended to satisfy the requirements of 314.50(d)(5)(vi). This analysis will include, at minimum, 16 weeks additional safety and efficacy data from Studies 101 and ALTA.

An integrated summary of safety (ISS) will be submitted with the initial clinical submission components and as a safety update in compliance with 21 CFR 314.50(d)(5)(vi). The ISS will include safety data of at least 355 patients with advanced solid tumors (including 297 ALK-positive NSCLC patients) enrolled in Studies 101 and ALTA, as well as data from 100 healthy volunteers enrolled in clinical pharmacology studies. Across Studies 101 and ALTA, ARIAD predicts that approximately 127 patients will have received brigatinib dosing regimen of 90 mg QD and approximately 141 patients will have received the brigatinib dosing regimen of 90 mg for 7 days followed by 180 mg QD. The ISS will present side by side comparisons of safety data from ALTA and 101. The safety data will include adverse events, exposure, laboratory data (chemistry, hematology), vital signs (heart rate, blood pressure), and ECGs. Data from these trials will not routinely be pooled. However, data will be pooled to summarize selected safety information including deaths within 30 days of study drug, serious adverse events, discontinuations due to study drug, and selected categories of AEs. ARIAD plans to pool data across different dose regimens and will provide more specifics to FDA during at the future Pre-NDA meeting.

GENERAL COMMENTS

As noted in FDA’s October 1, 2014, letter informing ARIAD that Breakthrough Therapy Designation for brigatinib was granted for the proposed designation, FDA advised ARIAD 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, as described in the MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy- Designated Drugs and Biologics at: http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm407009.pdf

Following this meeting, ARIAD is strongly encouraged to review their development program and ensure that requirements for submission of a complete application can be met for brigatinib.

FDA reminds ARIAD that the preliminary advice provided in FDA responses regarding content and format of the proposed NDA are intended as general advice to aid in decision-making. However, this advice does not constitute formal agreements reached regarding the content of a complete NDA under the PDUFA V Program. Please ensure that a pre-NDA CMC only meeting is held prior to the interdisciplinary pre-NDA meeting at which agreements reached under the PDUFA V Program will be captured.

Reference ID: 3795932
SPONSOR QUESTIONS AND FDA RESPONSES

Regulatory

1. Refer to Company Position on pages 22-32 in ARIAD’s background package.

   Can the Agency please comment on the proposed NDA submission plan for the initial accelerated approval as a treatment for patients with advanced, metastatic ALK+ NSCLC who have previously been treated with crizotinib described in the Company Position statement?

FDA Response:

The briefing document’s description of the proposed time line for meetings with FDA and schedule for submission in the rolling NDA appears acceptable with the following exceptions:

a. An integrated summary of safety (ISS) and an integrated summary of efficacy will be required for module 5.3.5.3.

b. In the NDA submission, include the cardiac safety report and QT data that incorporates comments and requests for additional information to be provided by the QT/IRT response to the ARIAD submission dated May 18, 2015, SDN 146.

c. A response from QT/IRT regarding the adequacy of the ARIAD proposed QT evaluation plan will be provided to ARIAD after a QT/IRT review of the submission dated May 18, 2015.

d. The proposal to include specific data on stability, updated efficacy and safety cannot be evaluated at this time. Agreement on the acceptability of the proposed approach will be made in discipline specific pre-NDA meetings.

ARIAD Response Received Via Email on June 30, 2015:

ARIAD believes that the analyses required under 21 CFR 314.50(d)(5)(v) describing a integrated summary of efficacy (ISE) can be adequately addressed in module 2.7.3 (Summary of Efficacy) with additional tables listings and figures required for these analyses provided in module 5.3.5.3. Additionally, ARIAD plans on taking similar approaches to pooling safety and efficacy data, with pooling limited to primary analyses of safety and efficacy taking into consideration the different populations, dose and dosing regimens, and the proportion of patients at the recommended dose in the 101 and ALTA trials. ARIAD will provide a more detailed plan for the development of the ISE (and ISS) in the pre-NDA meeting background materials.

Can FDA please comment on this general approach and describe what additional information would be helpful to include in the pre-NDA meeting briefing book to reach agreement on such an approach?
**Discussion During the Meeting:**
ARIAD clarified that full accrual in the ALTA trial is anticipated in September 2015, and the anticipated data cutoff date for the final efficacy analyses is approximately January 2016; data clean-up will require 3-6 months. ARIAD anticipates that between 10-20 patients will be dosed with the 90mg strength in the ALTA trial prior to the data cutoff date. In addition, ARIAD clarified that there are 45 patients in Study 101 remaining on treatment. The last patient was enrolled in July 2014, the data cutoff date for analysis of this study is approximately November 2015. FDA stated that the top-line results of the ALTA trial must be included in the briefing materials for the Multi-disciplinary pre-NDA meeting in order to allow FDA to reach agreements on the content and form of a complete application.

FDA requested an updated safety analysis for all patients providing overall adverse events and grade 3 and 4 adverse events by dosage regimen, with particular emphasis on the dosage regimens employed in the ALTA study, in the updated Investigator’s Brochure to be submitted in September 2015. With regards to early onset pulmonary events, FDA requested that the case definition should be submitted as early as possible, the elements comprising the case definition should supported by a summary of all such events observed to date. Use of a uniform case definition would support the systematic collection of data, in real-time, for patients currently in study 101 and ALTA.

**Chemistry, Manufacturing, and Control**

2. Refer to Company Position on pages 33-36 in ARIAD’s background package. ARIAD is currently developing a 90 mg tablet strength which has been added to the IND (IND 110935 Seq. 0143) for use in ongoing clinical trials. Subsequently, ARIAD intends to include both the 30 mg and 90 mg tablet strengths in the initial NDA submission. Can the Agency comment on the plan to support the introduction of the 90 mg tablet as described in the Company Position statement?

**FDA Response:**
The use of the 90 mg strength of brigatinib in approximately half of the brigatinib-treated patients enrolled in the ALTA trial precludes the need for bridging of the formulation to the earlier 30 mg formulations on efficacy grounds. However, in order to ascribe the pharmacokinetics of brigatinib, generated with the 30 mg strength formulations to the 90 mg strength, provide the following in the NDA:

a. A biowaiver request for the 90 mg strength.

b. Data demonstrating that the 90 mg and 30 mg strengths...

c. Comparative dissolution data of the 90 mg and 30 mg strengths demonstrating similar dissolution profiles. Use the f2 Similarity test or an alternative statistical test to demonstrate similarity in dissolution profiles of the formulations. Perform
the dissolution tests in the proposed medium and in three different pH media (pH 1.2, 4.5, 6.8).

Note that the proposed dissolution method must be evaluated and found acceptable by FDA before the comparative data in support of the biowaiver request will be deemed valid.

ARIAD Response Received Via Email on June 30, 2015:
ARIAD wishes to clarify that it is estimated that sparse PK assessments for the 90 mg strength would be gathered for approximately 10-20 patients in the ALTA study (see pages 28 and 34-35 in briefing book) not half of the patients as identified in the FDA pre-meeting feedback “approximately half of the brigatinib-treated patients enrolled in the ALTA trial precludes the need for bridging of the formulation to the earlier 30 mg formulations on efficacy grounds.” (see page 18 of FDA pre-meeting feedback).

Discussion During the Meeting:
FDA acknowledged the clarification. FDA stated that if adequate bridging is not established between the two strengths (30mg and 90mg) only the 30mg strength could be approved. ARIAD will request a subsequent discussion with FDA regarding their approach to bridging between the two strengths. ARIAD confirmed that the food effect study would be performed with the 90mg strength.

3. Refer to Company Position on page 37 in ARIAD’s background package.
ARIAD plans to submit, potentially, at least two separate Type B meeting requests that are focused on the chemistry, manufacturing and controls (CMC) aspects of the NDA and subsequent commercial launch. Can the Agency comment on the proposed approach for future CMC discussions and the proposed topics as described in the Company Position statement?

FDA Response:
The proposed topics for ARIAD’s meetings are acceptable. Depending on the nature of the questions for these meetings, other review disciplines may be consulted for the response.

ARIAD Response Received Via Email on June 30, 2015:
No additional discussion needed.

Non-Clinical

4. Refer to Company Position on pages 38-41 in ARIAD’s background package.
In prior meetings, the Agency has agreed that the planned nonclinical toxicology and absorption, distribution, metabolism, and excretion (ADME) studies identified in the Company Position are adequate to support the submission of an NDA for the initial accelerated approval for brigatinib as a treatment for advanced or metastatic ALK+ NSCLC who have previously been treated with crizotinib. Can the Agency
confirm that the package described in the Company Position continues to meet the Agency's submission expectations?

**FDA Response:**
In general the completed and planned pharmacology, safety pharmacology, and toxicology studies described in the meeting package appear sufficient to support NDA filing; however a final determination of the adequacy of the submitted data will be made at the time of original NDA submission. If ARIAD identifies any unique and important human metabolites during development, then additional toxicology studies may be required to support filing of an application. FDA emphasizes that if the results of the rat embryofetal development study are either negative or equivocal, ARIAD will need to conduct and submit the final report of a GLP-compliant embryofetal development study in rabbits as well in order to support the proposed marketing application.

**ARIAD Response Received Via Email on June 30, 2015:**
No additional discussion needed.

**Clinical Pharmacology**

5. Refer to Company Position on pages 42-44 in ARIAD’s background package. **In prior meetings, the Agency has agreed that the planned clinical pharmacology studies identified in the Company Position are adequate to support the submission of an NDA for brigatinib as a treatment for patients with advanced or metastatic ALK+ NSCLC who have previously been treated with crizotinib. Can the Agency confirm that the package described in the Company Position continues to meet the Agency's submission expectations?**

**FDA Response:**

a. Depending on the extent of inhibition or induction of the metabolism of brigatinib observed in the drug interaction trial (AP26113-15-105), ARIAD may need to assess the effect of moderate inhibitors and inducers of the relevant CYP isozyme. If needed, ARIAD can consider using PBPK modeling to predict the effect of moderate and weak inhibitors or inducers of CYP enzymes.

b. Details of the planned renal and hepatic trials were not provided. The planned and ongoing clinical trials need to adequately address the effect of varying levels of organ impairment. If a reduced study design is used in the dedicated organ impairment trials, additional assessments may be needed depending on the results of the trial. Refer to the FDA Guidances for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf and “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at:
c. Use the planned to-be marketed formulation in the planned pivotal food effect trial.

ARIAD Response Received Via Email on June 30, 2015:
No additional discussion needed.

Clinical

6. Refer to Company Position on page 45 in ARIAD’s background package.
As described the Company Position statement for Regulatory Question 1, ARIAD plans on requesting a rolling submission of the NDA to support the initial accelerated approval of brigatinib as a treatment for patients with advanced or metastatic ALK+ NSCLC who have previously been treated with crizotinib. Can the Agency comment on the proposed plan for analysis and presentation of the data from the brigatinib clinical development program as part of the rolling NDA submission?

FDA Response:
The proposal that safety and efficacy data from ALTA in the original NDA in which all patients have completed a minimum of 16 weeks follow up is acceptable. However, regarding the proposed plan for analysis and presentation:

a. The briefing document states that initial clinical data submission for this study will consist primarily of investigator-assessed responses. Although the primary efficacy endpoint of ALTA is investigator-assessed confirmed RECIST v1.1 ORR, an independent radiology review (IRR) will be required to corroborate investigator determined responses and duration of responses. Please see the Question 5 response from the Type B meeting minutes dated March 18, 2013.

b. The efficacy data presented in Table 27 of the briefing document does not include confirmed responses. FDA will rely upon confirmed responses for the determination of substantial evidence of effectiveness. Therefore the data should be presented as such.

c. Please see FDA’s response to Question 7 from the Type B meeting minutes dated March 18, 2013. PFS and OS, although secondary endpoints, are not interpretable in the context of a single arm trial and would not be included in product labeling and promotional materials.

d. For the Module 5 clinical datasets, please submit a “one patient per row” dataset consisting of key demographics and key efficacy endpoints.
e. If patients labeled as having “advanced” NSCLC, in fact, do not have metastatic disease, please identify those patients in both the clinical study reports (CSRs) and datasets.

**ARIAD Response Received Via Email on June 30, 2015:**
No additional discussion needed.

7. Refer to Company Position on page 46 in ARIAD’s background package.
The Company Position statement describes ARIAD’s top-line plans for the analysis of safety data from the brigatinib clinical development program that would support the submission of an NDA for the initial accelerated approval as a treatment for patients with advanced or metastatic ALK+ NSCLC who have previously been treated with crizotinib. Can the Agency please comment on the Company’s plans?

**FDA Response:**
The proposal to include data from at least 355 patients with advanced solid tumors (of whom 297 patients have ALK -positive NSCLC) in the ISS contained in the final module of the NDA is acceptable. FDA will reach agreement on the content of the three month update to the NDA when ARIAD provides details at the pre-NDA meeting.

During preparation of the proposed U.S. package insert (USPI) and CSRs, please note that FDA will require that treatment emergent laboratory abnormalities be presented by worst Grade in addition to “Grade shifts.”

**ARIAD Response Received Via Email on June 30, 2015:**
No additional discussion needed.

**FDA ADDITIONAL COMMENTS**

**Statistical:**

8. Please include in the submission:

a. SAS programs used to produce all results (tables, listings and figures) in “Section of Efficacy Evaluation” and “Section 14” of the product labeling.

b. SAS program(s) for deriving the ADaM datasets.

c. A define file (PDF and XML format) defining all the datasets and the variables (raw and the derived) providing a hyperlink to the algorithms used to derive the variables related to efficacy analysis. Any additional information regarding the data derivations not included in the define files must be provided in the “Reviewers Guide.”

**ARIAD Response Received Via Email on June 30, 2015:**
No additional discussion needed.
Biopharmaceutics:

9. FDA has the following comments regarding the dissolution information that should be provided in your NDA:

a. **Dissolution Method:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution development report should include the following information:

1) Solubility data for the drug substance over the physiologic pH range.

2) Detailed description of the dissolution test being proposed for the evaluation of the product and the developmental parameters (*i.e.*, selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for the product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e.*, no increase over 3 consecutive time-points) is reached. FDA recommends the use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45, 60, 90 and 120 min.

3) Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

4) Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (*i.e.*, ± 10-20% change to the specification-ranges of these variables).

5) Supportive validation data for the dissolution method (*i.e.*, method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

6) A list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.

b. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion (a) of the product, the following points should be considered:
1) The dissolution profile data (i.e., 15, 20, 30, 45, and 60 min) from the clinical batches and primary (registration) batches (throughout the stability program) should be used for setting the dissolution acceptance criterion (a) of the product.

2) The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.

3) The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

4) The selection of the specification time point should be where Q=80 % dissolution occurs.

5) A detailed discussion of the justification of the proposed dissolution acceptance criterion should be included in the appropriate section of the CTD.

c. **Data Presentation:** In the dissolution method development report, present detailed experimental data as follows:

1) Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.

2) In addition to the mean dissolution data presented in graphical and tabular formats in the dissolution development report, submit all individual vessel dissolution data for the clinical and registration/stability batches in “.xpt” format.

3) Batch release and stability dissolution data should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.

**ARIAD Response Received Via Email on June 30, 2015:**
No additional discussion needed.

**PREA-ARIAD Response Received Via Email on June 30, 2015:**
As noted in the background materials, ARIAD intends on submitting an orphan drug designation for “Treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer”. If granted, an orphan drug designation would render brigatinib exempt from the pediatric study requirements. However, it is unlikely that ARIAD would receive such a designation within the
next 60 days of the meeting; the time in which an Initial Pediatric Study Plan (iPSP) would be required.

**Can FDA please comment on the need to submit an iPSP and the content of an iPSP if required?**

**Discussion during meeting**

FDA stated ARIAD must submit an iPSP describing their plan to request a waiver from the full requirements of PREA because this drug for this indication has not been granted Orphan Drug Designation at this time.

**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 (iPSP) within 60 days of this meeting. 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](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.


**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: 

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 found at: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further discussion.

ACTION ITEMS

<table>
<thead>
<tr>
<th>Action Item/Description</th>
<th>Owner</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIAD should submit an updated safety analysis for all patients providing overall adverse events and grade 3 and 4 adverse events by dosage regimen with particular emphasis on the dosage regimens employed and the ALTA study in the updated IB.</td>
<td>ARIAD</td>
<td>Sept 2015</td>
</tr>
<tr>
<td>With regards to early onset pulmonary events, FDA requested that the Case Definition should be submitted as early as possible supported by a summary of all such events observed to date. This would support development of the systematic collection of data, in real-time, for patients currently in study 101 and ALTA.</td>
<td>ARIAD</td>
<td>Submit as early as possible</td>
</tr>
<tr>
<td>ARIAD will request a subsequent discussion with FDA regarding their approach to bridging between the 2 strengths.</td>
<td>ARIAD</td>
<td>TBD</td>
</tr>
<tr>
<td>ARIAD must submit an iPSP describing their plan to request a waiver from the full requirements of PREA because this drug for this indication has not been granted Orphan Drug Designation at this time.</td>
<td>ARIAD</td>
<td>Submit the Initial Pediatric Study Plan (iPSP) within 60 days of this meeting, August 28, 2015.</td>
</tr>
</tbody>
</table>

ATTACHMENTS AND HANDOUTS
No attachments or handouts for the meeting minutes.
OHOP’s End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

FDA’s methodology and submission structure for regulatory applications supports research study design, as indicated in the Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications and the Study Data Specifications. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor/applicant should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See SEND, SDTM and ADaM as referenced in Study Data Specifications). Study analyses datasets should be traceable to the tabulations datasets.

The PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors/Applicants should design and implement data standardization in all research protocols to be included in regulatory submissions, as required, based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor/applicant should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (CDASH) standard for design and implementation of data collection instruments.

The Study Data Specifications provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team. The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the Study Data Specifications, “prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file”.

In addition, please reference the CDER Common Data Standards Issues Document for further information on data standardization in submissions. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a
separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains.

Additional Links:

*Electronic Regulatory Submissions and Review Helpful Links*
*Electronic Common Technical Document (eCTD)*

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

<table>
<thead>
<tr>
<th><strong>GENERAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Special Protocol Assessment (SPA) Requests</strong></td>
</tr>
<tr>
<td>1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>SPA Requests for a Single Trial Intended to Support Marketing Approval</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.</strong></td>
</tr>
<tr>
<td>2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document:</td>
</tr>
<tr>
<td>- Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').</td>
</tr>
<tr>
<td>- A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.</td>
</tr>
</tbody>
</table>

| **Additional Content for SPA Request Submission** |
Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the
evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint.
   - If your trial uses an in vitro diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
     - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
     - Applicability of comparator treatment or of disease characteristics to U.S. population
   - Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format
## CLINICAL

1. Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.

2. Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.

3. Investigator instructions that may have been produced in addition to the protocol and investigator brochure.

4. All randomization lists and, if used, IVRS datasets (in SAS transport format)

5. All datasets used to track adjudications (in SAS transport format)

6. A Reviewers Guide to the data submission that includes, but is not limited to the following:
   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
   k) documentation of programs

7. Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).

8. Pediatric Studies:
   All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the FDA Pediatric Team at Pedsdrugs@fda.hhs.gov. You may also refer to the following FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

   The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation.
The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:


b) Safety endpoints for Adverse Events of Special Interest (AERI)

c) Definition of Treatment Emergent Adverse Event (TEAE)

d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter)

e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)

f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:


11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:
There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>a)</td>
<td>Site number</td>
</tr>
<tr>
<td>b)</td>
<td>Principle investigator</td>
</tr>
<tr>
<td>c)</td>
<td>Location: City State, Country</td>
</tr>
<tr>
<td>d)</td>
<td>Number of subjects screened</td>
</tr>
<tr>
<td>e)</td>
<td>Number of subjects randomized</td>
</tr>
<tr>
<td>f)</td>
<td>Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)</td>
</tr>
<tr>
<td>g)</td>
<td>Number of protocol violations (Major, minor, including definition)</td>
</tr>
</tbody>
</table>


18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
   a) subject age and gender
   b) signs and symptoms related to the adverse event being discussed
   c) an assessment of the relationship of exposure duration to the development of the adverse event
   d) pertinent medical history
   e) concomitant medications with start dates relative to the adverse event
   f) pertinent physical exam findings
   g) pertinent test results (for example: lab data, ECG data, biopsy data)
   h) discussion of the diagnosis as supported by available clinical data
   i) a list of the differential diagnoses, for events without a definitive diagnosis
   j) treatment provided
   k) re-challenge and de-challenge results (if performed)
   l) outcomes and follow-up information
   m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and
22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis.

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.

b) Exposure-Response Relationships – important exposure-response assessments.

c) Less common adverse events (between 0.1% and 1%).

d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.

e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.

f) Marked outliers and dropouts for laboratory abnormalities.

g) Analysis of vital signs focused on measures of central tendencies.

h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.

i) Marked outliers for vital signs and dropouts for vital sign abnormalities.

j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.

l) Standard analyses and explorations of ECG data.

m) Overdose experience.

n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

o) Explorations for:

i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

iv) Drug-demographic interactions

v) Drug-disease interactions

p) Drug-drug interactions
   i) Dosing considerations for important drug-drug interactions.
   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician’s Labeling Rule

Highlights

1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4) The drug name must be followed by the drug’s dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Indicon and Fantom).

6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5
sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).

7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

(a) “(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].

11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.

12) The Patient Counseling Information statement must appear in Highlights and must read “See 17 for PATIENT COUNSELING INFORMATION.” [See 21 CFR 201.57(a)(14)]

13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Table of Contents

15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
### 8.5 Geriatric Use (not 8.4)

20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “Sections or subsections omitted from the Full Prescribing Information are not listed.”

### Full Prescribing Information (FPI)

22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.


25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf)]

26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
<table>
<thead>
<tr>
<th>31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.</th>
</tr>
</thead>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TINA M ENNIS
07/22/2015
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD  20993

IND 110935

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

ARIAD Pharmaceuticals, Inc.
Attention: Andrew P. Slugg
Senior Director, Regulatory Affairs
26 Landsdowne Street
Cambridge, MA 02139-4234

Dear Mr. Slugg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AP26113.

We also refer to your August 11, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that AP26113 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, non-small cell lung cancer (NSCLC) whose tumors are resistant to crizotinib 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 AP26113 for the treatment of patients with ALK-positive, NSCLC whose tumors are resistant to crizotinib to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting². Please refer to the Guidance for Industry: Formal Meetings.

² [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

Reference ID: 3637932
between FDA or Sponsors and Applicants\textsuperscript{3} for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for AP26113 for treatment of patients with ALK-positive, NSCLC whose tumors are resistant to crizotinib is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Ingrid Fan, Regulatory Project Manager, at (301) 796-5053.

Sincerely,

\textit{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

\textsuperscript{3} http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
10/01/2014
LATE-CYCLE COMMUNICATION DOCUMENTS
Pre-Late Cycle Meeting Summary  
February 6, 2017

Application:  NDA 208772
Product:  Proposed as ALUNBRIG (brigatinib) Tablet, 30 and 90 mg
Submission Date:  August 29, 2016
Received Date:  August 29, 2016
Applicant:  ARIAD Pharmaceuticals Inc.

Proposed Indication:  ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Attendees:  Martha Donoghue, Steven Lemery, Naomi Horiba, Leah Her, Thomas Ly, Hong Zhao, Ruby Leong, Jiang Liu, Hongshan Li, Whitney Helms, Anwar Goheer, Joyce Crich, Steven Kinsley, Katherine Windsor, Joan Zhao, Janine Stewart, Carolyn McCloskey, Elizabeth Everhart, Rowe Medina, Lauren Iacono-Connor, Susan Thompson, Amy McKee, Karen Hennessy

1. Discipline Review Letters

Discussion:  No Discipline Review Letters have been issued to date.

2. Substantive Review Issues (by discipline)

Discussion:  The Team discussed the inspection findings at the imaging site. An IR will be issued regarding the IRC database changes. This issue will be added as an agenda topic to the tcon currently scheduled with ARIAD on 2/9/17. No issues were identified by any other disciplines.

3. Status of Information Requests

Discussion:  The Team was reminded that the revised PI is due 2/10/17. The Team confirmed that there are no outstanding IRs. No new IRs were planned to be for discussion at the late cycle meeting.

4. Advisory Committee Meeting

Discussion:  The Team discussed that an Advisory Committee Meeting is not planned. There are two SGEs currently scheduled for teleconferences on 2/28/17 and background package is expected to be sent in the week of 2/13/17.

5. REMS or other Risk Management Actions

Discussion:  The Team discussed that there were no REMS- or risk management plan-related issues. The final DRISK review was uploaded in DARRTS on 1/30/17.

6. Postmarketing Requirements/Commitments

Discussion:  The Team briefly discussed the newly identified clinical PMC regarding intracranial response rates in Study 201. A tcon with ARIAD to discuss this clinical PMC is scheduled for 2/9/17. Clinical and Clinical Pharmacology confirmed that ARIAD’s 1/5/17 and 1/6/17 responses to the PMRs and PMCs were acceptable. The Team confirmed that there were no additional PMRs/PMCs anticipated. The Team was reminded that PMR/PMC Development Templates should be finalized 4 weeks before the end of the review cycle.

Reference ID: 4078921
7. **Major Labeling Issues**

   **Discussion**: The Team was reminded that the revised PI is due from ARIAD on or before 2/10/17. The Team did not anticipate any discussion of the labeling during the LCM. The internal meeting to discuss the revised label is planned for 2/28/17.

8. **Review Plans to be communicated to Applicant during LCM**

   **Discussion**: The review is ongoing. The Team determined that an update will be provided on SGE, labeling, and PMR/PMC.

9. **Miscellaneous Items**

   **Discussion**: The Team was reminded that the LCM background package is due to ARIAD on or before 2/10/17.
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/s/

LEAH S HER
04/03/2017
NDA 208772

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Alunbrig (brigatinib) Tablets, 30 and 90 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 24, 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 Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Clinical Team Leader and Cross Discipline Team Leader (CDTL)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 24, 2017 / 11:00 – 12:00 PM (EST)
Meeting Location: White Oak 22 Room 1309

Application Number: NDA 208772
Product Name: brigatinib (proposed as ALUNBRIG)
Applicant Name: ARIAD Pharmaceuticals Inc.

Meeting Chair: Steven Lemery
Meeting Recorder: Leah Her

FDA ATTENDEES
Patricia Keegan    Director, DOP2
Martha Donoghue   Associate Director (Acting), DOP2
Steven Lemery     Clinical Team Leader, DOP2
Naomi Horiba     Clinical Reviewer, DOP2
Thomas Ly        Statistical Reviewer, DBV
Leah Her          Regulatory Health Project Manager, DOP2
Whitney Helms    Nonclinical Supervisor, DHOT
Hong Zhao        Clinical Pharmacology Team Leader, DCPV
Ruby Leong       Clinical Pharmacology Reviewer, DCPV
Joyce Crich      Product Quality Team Leader, OPQ
Doris Auth       DRISK Team Leader, OSE
Connie Cheng     DPVII Reviewer, OSE
Jonathan Goldsmith OND
Elin Mattsson    OGD (observer)

APPLICANT ATTENDEES
Melody Brown    Vice President, Regulatory Affairs (Takeda)
Daniel Bollag   Senior Vice President, Regulatory, Pharmacovigilance and Quality
Guilin Huang    Director, Regulatory Affairs
Shreya Mehta    Senior Associate, Regulatory Affairs
Tim Clackson    President of Research & Development, Chief Scientific Officer
Sergio Santillana Vice President, Clinical Research and Development, Chief Medical Officer
David Kerstein Senior Medical Director, Clinical Research and Development
Ming Jiang      Medical Director, Pharmacovigilance and Risk Management,
Ronald Knickerbocker Vice President, Biomedical Data Sciences & Information
Stephanie Lustgarten Senior Director, Biostatistics and Statistical Programming
Tim Maines      Vice President, Quality
Shirish Hirani  Vice President, Drug Development
Douglas Shorten Director, Program Management

Reference ID: 4069111
BACKGROUND

NDA 208772 was submitted on August 29, 2016, for brigatinib.

Proposed indication(s): ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

PDUFA goal date: April 29, 2017

FDA issued a Background Package in preparation for this meeting on February 10, 2017. On February 13, 2017, FDA confirmed that under Substantive Review Issues Identified to Date in the Background section, clinical item 2 had a typographical error and should have instead stated that “FDA is considering whether to include hypoglycemia hyperglycemia in the Warnings and Precautions section of the proposed labeling.”

DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion: FDA provided ground rules and objectives for the discussion as stated in the Late Cycle Background Package issued on February 10, 2017. No discussion occurred.

2. Discussion of Substantive Review Issues

- Review issues will be introduced by FDA and followed by a discussion.

Discussion: FDA reiterated concerns regarding verifiability of the IRC assessed data performed at . ARIAD stated that the responses to the February 7, 2017, information request, regarding IRC-assessed data performed at will be submitted during the week of February 27, 2017. FDA stated that the label may need to be adjusted based upon FDA’s review of the submitted responses.

FDA also reiterated that final labeling may include hyperglycemia in the Warnings and Precautions section. Inclusion of hyperglycemia would be based on the need to monitor for hyperglycemia and potentially treat hyperglycemia or dose modify brigatinib due to hyperglycemia. ARIAD may submit data regarding medical interventions required in patients who exhibited hyperglycemia in Study 201 to facilitate assessment of risk for potential labeling changes.
3. Information Requests

- On February 7, 2017, FDA issued an information request regarding data verification issues for the IRC database identified during the recent audit conducted by the Office of Scientific Investigations.

**Discussion:** Refer to item 2 above. No additional discussion occurred.

4. Postmarketing Requirements/Postmarketing Commitments

- **Clinical**
  a. **PMR:** Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of brigatinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

  | Study/Trial Completion: | March 31, 2020 |
  | Final Report Submission: | December 31, 2020 |

  **Discussion:** FDA inquired whether ARIAD intends to also use [b](4) for this proposed randomized trial (Study 301). ARIAD stated that they are using a different imaging vendor for Study 301.

  b. **PMC** for provision of mature follow-up data to better characterize duration of intracranial objective responses is under negotiation. Wording for this PMC has not yet been finalized.

  **Discussion:** FDA reiterated the Agency’s rationale for this request. FDA requested that the study completion date (i.e., the date used for the PMC milestone) be based upon the final efficacy analysis for this endpoint and should be justified based on the maturity of the data. ARIAD confirmed that the primary analysis for intracranial responses will be based upon IRC-assessed data. For the proposed PMC, ARIAD will provide milestones for the “Study Completion Date” and the “Final Report Submission Date.” ARIAD may also elect to include a “Final Protocol Submission” milestone date via the submission of a statistical analysis plan which could include ARIAD’s justification for the proposed study completion date.

- **Clinical Pharmacology / Pharmacometrics**
  c. **PMR:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity. Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for excessive drug toxicity may be acceptable.

  | Final Protocol Submission: | Not Applicable |
  | Study/Trial Completion: | Not Applicable |
  | Final Report Submission: | June 30, 2017 |
Discussion: No discussion occurred.

d. **PMR:** Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment.

Study/Trial Completion: September 30, 2017
Final Report Submission: June 30, 2018

Discussion: No discussion occurred.

e. **PMR:** Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment.

Study/Trial Completion: March 31, 2017
Final Report Submission: September 30, 2017

Discussion: No discussion occurred.

f. **PMC:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for decreased drug exposure may be acceptable.

Final Protocol Submission: Not Applicable
Study/Trial Completion: Not Applicable
Final Report Submission: June 30, 2017

Discussion: No discussion occurred.

g. **PMC:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations.

Final Protocol Submission: December 31, 2017
Study/Trial Completion: December 31, 2019
Final Report Submission: June 30, 2020

Discussion: No discussion occurred.

5. **Major labeling issues**

- On January 27, 2017, FDA provided comments to ARIAD’s proposed package insert.
• Additional labeling changes may be proposed by FDA after review of ARIAD’s response to the February 7, 2017, information request regarding data verification issues for the IRC database identified during the recent audit conducted by the FDA Office of Scientific Investigations.

Discussion: FDA acknowledged ARIAD’s February 10, 2017, revised package insert (PI) and responses to FDA’s request for information. FDA stated that the PI is currently under review.

6. Review Plans

• Discussions with SGEs – ongoing
• Labeling discussions – ongoing
• Finalization of above PMRs/PMCs – ongoing
• FDA Wrap-up meeting planned for March 24, 2017

Discussion: ARIAD inquired on additional actions or pending items. FDA stated that SGE discussions, labeling review, and finalization of the clinical PMC are outstanding. FDA will contact ARIAD should any issues arise that require discussion.

7. Wrap-up and Action Items

Discussion: The following action items were reiterated:

• ARIAD will provide a response to FDA’s February 7, 2017, clinical information request, by early week of February 27, 2017.
• ARIAD will submit proposed language and milestones for the clinical PMC regarding intracranial responses.

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.
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/s/

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STEVEN J LEMERY
03/15/2017
Hi Guilin,

Thanks for reaching out. Yes, it was a typo. It should be hyperglycemia- we will capture this correction in the late cycle meeting minutes.

Thank you,
Leah

Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov

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Guilin Huang, MBA, RAC
Director, Regulatory Affairs
ARIAD Pharmaceuticals, Inc.
125 Binney Street | Cambridge, MA 02142
Telephone: (617) 503-7074 | Mobile: (617) 503-7074
Email: Guilin.Huang@ariad.com

---

Hi Guilin,

Attached is the background package for our late cycle meeting scheduled for Friday, February 24, 2017.

Reference ID: 4069110
Kindly confirm receipt.

Regards,

Leah S. Her, MS, PMP
Regulatory Health Project Manager
FDA/CDER/OHOP/DOP2
Tel: 240-402-6611
Fax: 301-796-9849
Email: leah.her@fda.hhs.gov
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/s/

LEAH S HER
03/13/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208772

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
125 Binney Street
Cambridge, MA 02142

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Alunbrig (brigatinib) Tablets, 30 and 90 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 24, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at leah.her@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Leah Her, Regulatory Health Project Manager, at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 24, 2017 / 11:00 – 12:00 PM (EST)
Meeting Location: White Oak 22 Room 1309

Application Number: NDA 208772
Product Name: brigatinib (proposed as ALUNBRIG)
Indication: ALUNBRIG™ is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Applicant Name: ARIAD Pharmaceuticals Inc.

FDA ATTENDEES (tentative)
Jeffrey Summers Deputy Director for Safety, DOP2
Martha Donoghue Associate Director (Acting), DOP2
Steven Lemery Clinical Team Lead, DOP2
Naomi Horiba Clinical Reviewer, DOP2
Kun He Statistical Team Lead, DBV
Thomas Ly Statistical Reviewer, DBV
Susan Thompson OSI Team Lead, GCPAB
Lauren Iacono-Conner OSI Reviewer, GCPAB
Karen Hennessy Safety Regulatory Project Manager, DOP2
Leah Her Regulatory Health Project Manager, DOP2

APPLICANT ATTENDEES
To be determined

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 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, we may not be prepared to discuss that new information at this meeting.
SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date and none are expected at this time.

Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical / Office of Scientific Investigations

1. The preliminary findings of the inspection of CRO (b)(4) the vendor who conducted the blinded central imaging review for Study AP26113-13-201, indicate that a substantial amount of the study data changes for imaging assessment time points could not be verified.

An information request regarding these changes to entries in the IRC database was submitted to ARIAD on February 7, 2017 and follow-up discussion regarding this issue occurred during a February 9, 2017 teleconference between FDA representatives and ARIAD. During this teleconference, FDA emphasized the importance of a timely, complete, and accurate response to this information request, and ARIAD stated that the requested information is currently being gathered.

Upon review of the requested information, FDA will determine the appropriate action(s) to take based on these findings (which could include changes to labeling or a request for further independent audit of the images).

2. FDA is considering whether to include hypoglycemia in the Warnings and Precautions section of the proposed labeling.

3. FDA and ARIAD are in the process of negotiating an additional Post Marketing Commitment (PMC) for the provision of mature data from Study AP26113-13-201 to better inform labeling regarding the duration of intracranial responses. During the February 9, 2017 teleconference, ARIAD agreed to submit a proposal for this PMC via e-mail for FDA review and internal discussion.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned; however, two Special Government Employees (SGEs), comprising a medical oncologist and a patient advocate, will be separately consulted.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.
Late Cycle Meeting (LCM) AGENDA

1. Introductory Comments – 5 minutes

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 25 minutes

- Review issues will be introduced by FDA and followed by a discussion.

3. Information Requests – 5 minutes

- On February 7, 2017, FDA issued an information request regarding data verification issues for the IRC database identified during the recent audit conducted by the Office of Scientific Investigations.

4. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- Clinical
  a. PMR: Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of brigatinib over available therapy in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

  | Study/Trial Completion: | March 31, 2020 |
  | Final Report Submission: | December 31, 2020 |

  b. PMC for provision of mature follow-up data to better characterize duration of intracranial objective responses is under negotiation. Wording for this PMC has not yet been finalized.

- Clinical Pharmacology / Pharmacometrics
  c. PMR: Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib to address the potential for excessive drug toxicity. Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for excessive drug toxicity may be acceptable.

  | Final Protocol Submission: | Not Applicable |
  | Study/Trial Completion: | Not Applicable |
  | Final Report Submission: | June 30, 2017 |

  d. PMR: Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment.

  | Study/Trial Completion: | September 30, 2017 |
  | Final Report Submission: | June 30, 2018 |
e. **PMR:** Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment.

   Study/Trial Completion: March 31, 2017
   Final Report Submission: September 30, 2017

f. **PMC:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of brigatinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Alternatively, use of a physiologically-based pharmacokinetic modeling approach to address the potential for decreased drug exposure may be acceptable.

   Final Protocol Submission: Not Applicable
   Study/Trial Completion: Not Applicable
   Final Report Submission: June 30, 2017

g. **PMC:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of brigatinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) to assess the magnitude of decreased exposures of a sensitive CYP3A4 substrate and to determine appropriate dosing recommendations.

   Final Protocol Submission: December 31, 2017
   Study/Trial Completion: December 31, 2019
   Final Report Submission: June 30, 2020

5. **Major labeling issues – 5 minutes**
   - On January 27, 2017, FDA provided comments and proposed revisions to the draft brigatinib package insert to ARIAD.

   - Additional labeling changes may be proposed by FDA after review of ARIAD’s response to the February 7, 2017, information request, regarding data verification issues for the IRC database identified during the recent audit conducted by the FDA Office of Scientific Investigations.

6. **Review Plans – 5 minutes**
   - Discussions with SGEs – ongoing
   - Labeling discussions – ongoing
   - Finalization of above PMRs/PMC s – ongoing
   - FDA Wrap-up meeting planned for March 24, 2017

7. **Wrap-up and Action Items – 5 minutes**
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/s/

MARTHA B DONOGHUE on behalf of PATRICIA KEEGAN
02/10/2017