CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208772Orig1s000

Trade Name:	Alunbrig Tablets, 30 and 90 mg
Generic or Proper Name:	brigatinib
Sponsor:	ARIAD Pharmaceuticals, Inc.
Approval Date:	April 28, 2017
Indication:	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.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208772

ACCELERATED APPROVAL

ARIAD Pharmaceuticals, Inc.
Attention: Guilin Huang, M.B.A., R.A.C.
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, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alunbrig (brigatinib) tablets, 30 and 90 mg.

This new drug application provides for the use of Alunbrig (brigatinib) tablets, 30 and 90 mg for 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208772**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

Based on the provided stability data, a 24-month expiration dating period is granted for 30 mg Alunbrig (brigatinib) tablets, and a 18-month expiration dating period is granted for 90 mg Alunbrig (brigatinib) tablets, from the date of manufacture of the tablets in the proposed commercial container closure systems when stored at USP controlled room temperature 20 to 25ºC (68 to 77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF).

ADVISORY COMMITTEE

Your application for brigatinib was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in this intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submissions dated January 5, 2017 and March 28, 2017. This requirement, along with required completion dates, is listed below.

3190-1 Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of brigatinib in patients with metastatic anaplastic lymphoma kinase positive non-small cell lung cancer (NSCLC).

Trial Completion:	March 2020
Final Report Submission:	December 2020

We acknowledge submission of the protocol to IND 110935 on November 15, 2015. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of toxicity due to drug-drug interactions of Alunbrig (brigatinib) with inhibitors of CYP3A4.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3190-2 Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose pharmacokinetics of brigatinib, to assess the potential for excessive drug toxicity.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Final Report Submission: June 2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of a serious risk of toxicity from drug over-exposure due to the effect of impaired hepatic or renal function on the pharmacokinetics of Alunbrig (brigatinib).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3190-3 Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with renal impairment.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Trial Completion: September 2017
Final Report Submission: June 2018

3190-4 Complete a clinical pharmacokinetic trial to determine an appropriate dose of brigatinib to minimize toxicity in patients with hepatic impairment.

The timetable you submitted on January 6, 2017 states that you will conduct this trial according to the following schedule:

Trial Completion: March 2017 (completed)
Final Report Submission: September 2017

Submit clinical protocols to your IND 110935 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3190-5 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 submitted on March 15, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	September 2017
Final Report Submission:	March 2018

3190-6 Conduct a physiologically-based pharmacokinetic modeling study 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.

The timetable you submitted on January 6, 2017, states that you will conduct this trial according to the following schedule:

Final Report Submission:	June 2017

3190-7 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.

The timetable you submitted on January 6, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2017
Trial Completion:	December 2019
Final Report Submission:	June 2020

Submit clinical protocols to your IND 110935 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (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).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application within two weeks of receipt of this communication.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
04/28/2017