

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208434Orig1s000

OTHER REVIEW(S)

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Complete a pharmacokinetic trial to determine an appropriate dose of alectinib in patients with moderate to severe hepatic impairment 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."

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

Other

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for NDAs)

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/s/

STACY S SHORD
12/07/2015

HONG ZHAO
12/07/2015
I concur.

JEFFERY L SUMMERS
12/08/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

ADDENDUM CLINICAL INSPECTION SUMMARY

DATE: December 2, 2015

TO: Gina Davis, Regulatory Project Manager
Erin Larkins, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 208434

APPLICANT: Hoffmann-La Roche Inc.

DRUG: Alecensa (alectinib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of ALK positive non-small cell lung cancer

CONSULTATION REQUEST DATE: July 10, 2015
INSPECTION SUMMARY GOAL DATE: November 6, 2015
DIVISION ACTION GOAL DATE: December 18, 2015
PDUFA DATE: March 2, 2016

ADDENDUM to Clinical Inspection Summary:

This is an addendum to the Clinical Inspection Summary (CIS) for NDA 208434, dated November 2, 2015. The basis for this addendum is to provide an interim classification for the inspection of Dr. Sai-Hong Ou, and an assessment of the Site's data integrity. Nothing else in the original CIS, dated November 2, 2015, has changed. At the time the Clinical Inspection Summary (CIS) was finalized, the clinical inspection of Dr. Ou was still ongoing and it was unclear as to how long the inspection would continue. As such, the CIS was finalized with only limited information and without a preliminary determination of data reliability for Dr. Ou's site.

Based upon preliminary communications with the FDA field investigator after the close-out of the inspection, the interim classification for Dr. Ou's site is Voluntary Action Indicated (VAI). The reliability of data for Dr. Ou's site, associated with Study NP28761 and Study NP28673, submitted to the Agency in support of NDA 208434 appear reliable.

Updated Information: The final Established Inspection Report (EIR) for the inspection of Dr. Ou's site is still pending. OSI indicated in the CIS dated November 2, 2015, that an addendum to the CIS would be generated after the final review of the EIR for Dr. Ou's site. The inspection was completed on November 3, 2015 and the FDA field investigator has since provided preliminary information regarding inspectional findings after the inspection close-out. DOP2 CDTL Gideon Blumenthal requested via email on November 27th, 2015 that OSI amend the CIS for NDA 208434 to include an interim classification for the inspection of Dr. Ou's site based upon the latest preliminary information.

With respect to Study NP28761, the site screened 36 subjects and 27 were enrolled (18 Subjects into Phase I and a subset of 9 Subjects were subsequently enrolled into Phase II). At the time of this inspection there were 12 subjects still on study treatment, 5 in follow-up, 1 subject had transferred to another study site, 2 subjects were lost to follow-up, and 8 subjects had died. The study records of 10 subjects were audited in depth. A partial review of the remaining 18 subject files for AEs and primary efficacy endpoint data was also conducted. With respect to Study NP28673, the site screened 6 subjects and 5 were enrolled. At the time of this inspection 3 subjects had completed the study and 1 had died. The study records of 5 subjects enrolled were audited in depth.

The primary efficacy endpoint for both studies is based on an Independent Review Committee (IRC) imaging review for tumor response per RECISTS1.1. Therefore, corroborating efficacy evidence was reviewed at the site that included records of the tumor scans sent to the IRC vendor. In addition, the FDA field investigator reviewed the efficacy endpoint data as determined by the investigator and found no discrepancies with that reported in NDA 208434.

With respect to AE reporting, for study NP28761 there was one instance where an SAE was reported to the sponsor outside of the protocol specified reporting window, “within 24 hours of the investigator becoming aware of the event”.

There were some missed protocol-specified periodic assessments and minor documentation issues. A Form FDA 483 was issued citing one inspectional observation. Below are examples of inspectional findings. Samples below are limited to the dataset cut-off dates for each protocol.

Observation 1. An Investigation was not conducted in accordance with the signed statement of investigator and investigational plan. For example,

A. Protocol NP28761

1. Subjects 10615 and 10618 were enrolled into the study (Phase I) even though they met Phase I Portion Specific Exclusion Criteria #3, “*History of cholecystectomy*”. Neither of these subjects enrolled into the Phase II portion of the study.
 - a. Subject 10615 had gallbladder surgery in March 2012 and was enrolled into the study on June 3, 2013
 - b. Subject 10618 had gallbladder surgery in 2002 and was enrolled into the study on June 21, 2013.
2. Subject 10605 was enrolled into the study but did not meet Inclusion Criteria #9, “Adequate renal function as defined by: Serum creatinine $\leq 1.5 \times$ ULN and Calculated creatinine clearance of ≥ 60 mL/min. Subject 10605 had a calculated creatinine clearance of 43.58 mL/min as documented on the screening visit laboratory report dated February 19, 2013. This subject was subsequently enrolled (November 12, 2013) into Phase II of the study.
3. Protocol section 8.4.1, "Screening Period for both Phase 1 and Phase II Portions" includes laboratory assessments for hematology, serum chemistry, and blood coagulation tests be performed for each required visit. This was not always done. For example,
 - a. Subject 10614 did not have a required laboratory assessment for blood urea nitrogen at Cycle 3 Day 1, July 13, 2013. This subject was subsequently enrolled into Phase II of the study
 - b. Subject 20609 did not have the following required laboratory assessments performed. This subject was subsequently enrolled into Phase II of the study.
 - i. Direct bilirubin at Cycle 1 Day 1 (April 24, 2014) and Cycle 1 Day 8 (April 30, 2014).
 - ii. Basophils at Cycle 2 Day 1 (May 15, 2014) and Cycle 3 Day 1 (June 5, 2014).
4. One subject out of 10 reviewed had an SAE that was not reported within 24 hours of the site becoming aware of the event. Subject 10617 was hospitalized from [REDACTED] ^{(b) (6)} for bronchitis. The site became aware of the SAE on December 12, 2013 during the Cycle 9 visit. The SAE was not reported to the sponsor until April 18, 2014. Subject 10617 was not enrolled into the Phase II portion of the study.

B. Protocol NP28673

1. Subject 259878202 did not have the following protocol specified laboratory assessments performed.
 - a. Phosphorus, magnesium, CPK, and GGT at Cycle 6 on May 1, 2014.
 - b. CPK and GGT at Cycle 7 on May 27, 2014 and at Cycle 8 on June 24, 2014.
 - c. Phosphorus, magnesium, CPK, and GGT at Cycle 9 on July 22, 2014.
2. Subject 259878203 did not have the following protocol specified laboratory assessments performed.
 - a. PT (or INR) and aPTT at Cycle 1 Day 8 on December 19, 2013, Cycle 1 Day 15 on December 26, 2013, Cycle 2 on January 7, 2014, and Cycle 3 on February 6, 2014.
 - b. CPK and GGT at Cycle 4 on March 5, 2014, Cycle 6 on April 30, 2014 and Cycle 8 on June 25, 2014.
3. Per Protocol Version 3, Section 4.4.1.4, and Protocol Version 5, Section 4.4.1.5 titled "Vital Signs", specifies that vital signs will include measurements of respiratory rate, oxygen saturation (SpO₂), pulse rate, systolic and diastolic blood pressure, and temperature. All 5 subjects enrolled into the study did not have SpO₂ measured for each required visit. For example,
 - a. Subject 259878202 did not have a recorded SpO₂ at the following study visits; Cycle 3 on February 4, 2014 through Cycle 9 on July 22, 2014. This subject had at least 23 treatment cycles.
 - b. Subject 259878204 did not have a recorded SpO₂ at the following study visits; Screening on December 10, 2013, EOT on May 20, 2014, and at the 28 Day Follow-Up on June 4, 2014.

OSI Reviewer Note: A written response to the Form FDA 483 inspectional observations from Dr. Ou is expected but has not yet been received. In general, the protocol violations, found at this site should not importantly impact overall study outcomes and in particular should not have placed subjects at risk. The missed assessments appear to have been performed at other study visits both before and after the study visit where the laboratory test was missed. Subject 10605 was enrolled into Study NP28761 with a calculated creatinine clearance of 43.58 mL/min, thus, did not meet Inclusion Criteria #9 (Adequate renal function). Subject 10605 received 6 treatment cycles in the Phase I portion of the study and a subsequent 17 treatment cycles in the Phase II portion of the study.

Assessment of data integrity: Notwithstanding the inspectional observations noted above, the data for Dr. Ou's site, for Study NP28761 and Study NP28673 submitted to the Agency in support of NDA 208434, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{ See appended electronic signature page }

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/s/

LAUREN C IACONO-CONNORS
12/02/2015

SUSAN D THOMPSON
12/02/2015

KASSA AYALEW
12/02/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 18, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 208434
Product Name and Strength: Alecensa (Alectinib) Capsules, 150 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Hoffmann La-Roche
Submission Date: July 6, 2015, September 17, 2105, and November 13, 2015
OSE RCM #: 2015-1397
DMEPA Primary Reviewer: Grace P. Jones, PharmD, BCPS
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the New Drug Application approval process for Alecensa, we reviewed the proposed container label, carton labeling, and Prescribing Information (PI) for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The container closure system for the proposed Alecensa capsules consists of a bottle with a (b) (4) screw cap that contains an integrated desiccant within the screw cap. The Applicant is proposing a single bottle count size of 240 capsules. The proposed dosing schedule for Alecensa includes the starting dose 600 mg twice daily (240 capsules for a 30 day supply), a first reduction of 450 mg twice daily (180 capsules), and a second and final dose reduction of 300 mg twice daily (120 capsules). The dose reductions require dispensing 120 or 180 capsules from the 240-count original bottle. However, the language in the proposed PI Section 16 states to “Store in the original container to protect from light and moisture”. Thus, we requested information from the Applicant regarding if the proposed product is required to be stored in the original container then how would the capsules be dispensed for dose reductions (see DARRTS Labeling Discussion, dated October 26, 2015). In the Applicant’s response, they recommended Alecensa to be prescribed and dispensed in a whole bottle unit to ensure the integrity of the drug product (see DARRTS Quality/Response to Information Request, dated November 3, 2015). Because to prescribe and dispense Alecensa in a whole 240-count bottle unit only is not realistic given the proposed dose reduction and current prescribing practice, we do not think the Applicant’s response addressed our concerns. Per discussion with OPQ, if the

capsules are not kept in the original manufacturer bottle then the capsule shells will stick to each other due to moisture. Therefore, a postmarketing commitment (PMC) for a bottle count size of 60 capsules is being recommended (see DARRTS Internal Meeting Minutes, dated November 13, 2015). This PMC would accommodate both dose reductions of 450 mg twice daily and 300 mg twice daily, such that for a 30-day supply, three of the 60-count bottles and two 60-count bottles would be provided to the dose reduction schedules respectively. Proposing a PMC for a 60 capsule bottle count size would also ensure the integrity and stability of the container closure system of the proposed Alecensa capsules, either in 240-count size or in the proposed PMC 60-count size. In addition to a 60-count bottle, DMEPA is open to other packaging configurations such as blister packs too, as long as the packaging configuration can provide for the appropriate dispensing of 120 and 180 capsules.

Our review of the Prescribing Information that was submitted on November 13, 2015 determined it appears acceptable from a medication error perspective.

Overall, the proposed container label and carton labeling appears acceptable from a medication error perspective, however, the image of the capsule in the carton labeling can be improved to reflect the actual representation of the capsule.

4 CONCLUSION & RECOMMENDATIONS

The proposed PMC of a 60-count bottle size accommodates capsule quantity for dose reduction schedules while preserving the integrity of the proposed Alecensa container closure system. The proposed container label and carton labeling can be improved to provide clarity and promote safe use of the product.

4.1 RECOMMENDATIONS FOR HOFFMANN LA-ROCHE

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

Carton Labeling

- Ensure that the [REDACTED] (b) (4)

Container Label and Carton Labeling

- Revise the [REDACTED] (b) (4) statement on the side panels to read, “**Usual dosage:** See prescribing information”.

¹ Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Alecensa that Hoffmann La-Roche submitted on July 6, 2015.

Table 2. Relevant Product Information for Alecensa	
Initial Approval Date	N/A
Active Ingredient	Alectinib
Indication	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on, or are intolerant to crizotinib
Route of Administration	Oral
Dosage Form	Capsules
Strength	150 mg
Dose and Frequency	600 mg orally twice daily with food (starting dose) Dose reductions: 450 mg orally twice daily (first dose reduction) 300 mg orally twice daily (second dose reduction)
How Supplied	Bottles of 240 capsules
Storage	Do not store above 30°C (86°F) Store in the original container to protect from light and moisture
Container Closure	Round, white 250 mL high-density polyethylene (HDPE) bottle with a child-resistant, (b) (4) screw cap and an integrated desiccant

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Alecensa labels and labeling submitted by Hoffmann La-Roche on July 6, 2015.

- Container label
- Carton labeling
- Prescribing Information (July 6, 2015, September 17, 2015, and November 13, 2015)

G.2 Label and Labeling Images

Container Label



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

GRACE JONES
11/18/2015

CHI-MING TU
11/18/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 19, 2015

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ALECENSA (alectinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 208434

Applicant: Hoffmann-La Roche, Inc. c/o Genentech, Inc.

1 INTRODUCTION

On July 6, 2015, Hoffmann-La Roche, Inc. c/o Genentech, Inc. submitted for the Agency's review the final portion of a rolling submission for an original New Drug Application (NDA) 208434 for ALECENSA (alectinib) capsules. The proposed indication for ALECENSA (alectinib) capsules is for the treatment of anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on crizotinib.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on July 14, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ALECENSA (alectinib) capsules.

2 MATERIAL REVIEWED

- Draft ALECENSA (alectinib) PPI received on July 6, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2015.
- Draft ALECENSA (alectinib) Prescribing Information (PI) received on July 6, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2015.
- Approved ZYKADIA (ceritinib) comparator labeling dated July 22, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
11/19/2015

NAZIA FATIMA
11/19/2015

BARBARA A FULLER
11/19/2015

LASHAWN M GRIFFITHS
11/19/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information**

Memorandum

Date: 11/19/2015

To: Gina Davis MT (ASCP)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Alecensa (alectinib) capsule
208434

Office of Prescription Drug Promotion Comments on proposed
labeling (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) for alectinib as requested in consult from Division of Oncology Products 2 (DOP2) dated July 14, 2015.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "NDA 208434-Roche's redline-text of 11.12.15" sent via electronic mail on November 16, 2015 to OPDP from DOP2 (Gina Davis). OPDP's comments are provided directly in the marked-up version of the label attached below. OPDP has reviewed the carton/container labeling send via electronic mail on November 19, 2015 from DOP2 (Gina Davis) and has no comments at this time. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed PPI were provided under a separate cover on November 19, 2015 and are based on the draft labeling titled, "NDA 208434-roche-9.17.15 gd Labeling counter proposal.dox.docx" send via electronic mail on November 5, 2015 to OPDP from DOP2 (Gina Davis).

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
11/19/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: October 3, 2015

From: Suchitra M. Balakrishnan, MD, PhD., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Oncology Products-2 (DOP2)

Drug: ALECENSA (alectinib)

NDA/BLA: 208434

Applicant: Hoffmann-La Roche, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed
Indication: For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).

Materials Reviewed:

- Consult request dated July 10, 2015 (DARRTS reference ID 3792219)
- Applicant proposed labeling dated July 6, 2015

Consult Question:
Request review of the alectinib label and the patient package insert.

INTRODUCTION

Hoffman-La Roche Inc., have submitted a new drug application (NDA) for Alecensa (alectinib) on July 6, 2015. The proposed indication is for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The Agency granted Breakthrough Therapy Designation for alectinib on June 26, 2013, and orphan drug designation was granted on January 27, 2015. Priority review was also granted with a planned action date of December 18, 2015.

DOP2 consulted DPMH to review the proposed labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND

Alectinib Drug Characteristics:

Alectinib is a small molecule (molecular weight 519 g/mol) that is a selective inhibitor of anaplastic lymphoma kinase (ALK) and “rearranged during transfection” (RET) tyrosine kinase. Alectinib inhibits ALK tyrosine kinase and blocks downstream signaling pathways, such as STAT3, PI3K/AKT and MAPK¹ to induce tumor cell death (apoptosis). Currently approved drugs in the same class include crizotinib (Xalkori) and ceritinib (Zykadia).

Alectinib is approved and marketed in Japan for use in patients with ALK-positive unresectable, recurrent or advanced NSCLC at a dose of 300 mg BID. The proposed dose outside of Japan is 600 mg BID. Based on Population-PK analysis, following BID administration of 600 mg, steady-state was achieved after 6.75 days. The volume of distribution after multiple dosing was 4,016 L for alectinib and 10,093 L for major metabolite M4, indicating extensive distribution into tissues. The geometric mean apparent half-life (T_{1/2}) estimated by the population-PK model was 32.5 and 31 hours for alectinib and M4, respectively ².

Non- small Cell Lung Cancer:

Lung cancer is the second most common cancer and the primary cause of cancer-related death in both men and women in the United States. Approximately 6.6 percent of men and women will be diagnosed with lung and bronchus cancer at some point during their lifetime, based on 2010-2012 data. The median age at diagnosis is 70 years³. NSCLC is the most common type of lung cancer and comprises 85% of lung cancers⁴. Survival rates for lung cancer tend to be much lower than for other common cancers, as a result of late diagnosis and limited effective therapy in advanced stages of the disease. The expected 5-year survival rate for all lung cancer patients is only 17%, compared with 65% for colon cancer, 90% for breast cancer, and 99% for prostate cancer⁴

1 Kodama T, Tsukaguchi T, Yoshida M, Kondoh O, Sakamoto H. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett* 2014;351:215-221.

2 Applicant's Clinical Overview, eCTD 2.5

3 <http://seer.cancer.gov/statfacts/html/lungb.html>

4 <http://www.cancer.org/cancer/lungcancer/index>

Approximately 5% of patients with NSCLC have tumors harboring a rearranged ALK gene/fusion protein⁵. Patients with “ALK-positive” tumors (tumors harboring a rearranged ALK gene/fusion protein) tend to have specific clinical features, including never or light smoking history, younger age, adenocarcinoma, and sensitivity to therapy with ALK kinase inhibitors⁶.

NSCLC and Pregnancy:

Although lung cancer is one of the most common malignancies in the U.S. general population, it is rare during pregnancy⁷.

Approximately 60 cases of lung cancer in pregnancy are reported in the literature, including nine cases registered in the International Cancer in Pregnancy registration study. NSCLC, predominantly of adenocarcinoma type, accounted for the majority of histological diagnosis (77–87%)⁸. Almost all patients presented with advanced disease, with poor overall survival (less than half of mothers alive three months after delivery) and low response rate to cytotoxic chemotherapy. There are five cases of patients treated with tyrosine kinase inhibitors during pregnancy reported in the literature. Three patients were treated with erlotinib (two of them during an unrecognized pregnancy), one received gefitinib and the last patient crizotinib without maternal objective responses. Neonates were born without reported congenital malformations^{9,8}.

As discussed earlier, patients harboring a rearranged ALK gene/fusion protein tend to be younger and therefore, can be of childbearing potential.

Pregnancy and Nursing Mothers Labeling:

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling

5 Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. *Clin Cancer Res*. 2011; 17(8):2081 - 6.

6 Ou SHI, Bartlett CH, Mino-Kenudson M, et al. Crizotinib for the Treatment of ALK Rearranged Non-Small Cell Lung Cancer: A Success Story to Usher in the Second Decade of Molecular Targeted Therapy in Oncology. *Oncologist* 2012;17:1351 -75

7 Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer* 2006;42:126–40.

8 Boussios S, Han SN, Fruscio R, Halaska MJ, Ottevanger PB, Peccatori FA, et al. Lung cancer in pregnancy: report of nine cases from an international collaborative study. *Lung Cancer* 2013;82:499–505.

9 Efficacy and safety of gefitinib during pregnancy: Case report and literature review. S. Gil, J. Goetghelucka,, A. Paci, S. Broutin, S. Friard, L.J. Couderc, J.M. Ayoubi, O. Picone, C. Tcherakian.

10 *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014). *Lung Cancer* 85 (2014) 481–484

Rule¹¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Non-clinical Experience:

The information below is based on the applicant's non-clinical overview and labeling discussions with the Pharmacology-Toxicology reviewers. For further details, the reader is referred to the final Pharmacology-Toxicology review by Dr. Eias Zahalka, Ph.D.

As per the ICH S9 guidelines, studies on (1) fertility and early embryonic development and (2) pre- and post-natal toxicology were not required for alectinib. Only preliminary studies were conducted.

In a rabbit preliminary embryofetal study, administration of alectinib by oral gavage during the period of organogenesis resulted in abortion or complete embryo-fetal mortality at the maternally toxic dose of 27 mg/kg/day (approximately 2.9-fold the estimated human AUC_{ss,24} with alectinib 600 mg BID) in three of six rabbit litters. The remaining three litters in this group had few live fetuses, decreased fetal and placental weights, and retroesophageal subclavian artery.

In a rat preliminary embryofetal development study, administration of alectinib during organogenesis by oral gavage resulted in complete litter loss in all pregnant rats at 27 mg/kg/day (approximately 4.5-fold the estimated human AUC_{ss,24} with alectinib 600 mg BID). Doses greater than or equal to 9 mg/kg/day (approximately 2.7-fold the estimated human AUC_{ss,24} with alectinib 600 mg BID), resulted in maternal toxicity as well as developmental toxicities including decreased fetal weight, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae

Alectinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but induced an increase in numerical aberrations in the *in vitro* cytogenetic assay using Chinese hamster lung cells with metabolic activation and increased micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes

Effects on male reproductive organs were observed in general toxicology studies conducted in rats and monkeys. In rats, glandular atrophy was reported in the prostate, and seminal vesicles at doses resulting in exposures approximately 2.4 times the estimated human AUC with alectinib 600 mg BID. In monkeys, interstitial fibrosis of the testis was observed at 12 mg/kg (approximately 0.2 times the estimated human AUC with alectinib 600 mg BID).

No studies evaluating the effect of alectinib on lactation were conducted.

¹¹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

**Clinical Experience:
Alectinib and Pregnancy:**

Given the known embryotoxic effects based on mechanism of action of alectinib and non-clinical findings, females of reproductive potential in the clinical studies had to use effective contraception. A search of published literature for available human pregnancy data was performed, to update the Pregnancy subsection of labeling for alectinib, and no studies were found.

DPMH Assessment:

Although human pregnancy outcome data are not available for alectinib, consistent with other tyrosine kinase inhibitors, alectinib is potentially genotoxic and teratogenic based on the drug's mechanism of action and data from animal studies. Patients should be advised about the potential risk to the fetus.

Alectinib and Lactation:

The applicant did not provide human data on the use of alectinib during lactation. The Drugs and Lactation Database (LactMed¹²) and Pubmed were searched for available lactation data on the use of alectinib, ceritinib or crizotinib, and no information was found. Serious adverse reactions (hepato-toxicity, interstitial lung disease, bradycardia, and CPK elevation with myalgias) were observed in adult patients in clinical trials with alectinib.

DPMH Assessment:

The characteristics of alectinib suggest that alectinib may be present in breast milk. Although alectinib has a low bioavailability (37%), the drug has a molecular weight of 519 Daltons (Drugs with molecular weights less than 800 Daltons can easily pass into breast milk), volume of distribution of over 4000L and a long half-life of 32.5 hours, which increases the presence of the drug in the mother's circulation and may increase infant exposure to the drug via breast milk¹³.

Proposed alectinib lactation labeling states that the drug is not recommended during breastfeeding. Given the risk of potential serious adverse events seen in adult patients in clinical trials with alectinib, breastfeeding with maternal use of alectinib is not recommended due to the potential for serious adverse reactions in a breast-fed infant. DPMH agrees with the applicant's recommendation against breastfeeding during treatment with alectinib.

¹²<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹³ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

Females and Males of Reproductive potential:

Although there were no human or animal studies conducted to evaluate the effect of alectinib on fertility, results from the repeat-dose toxicity studies in rats and monkeys suggest that alectinib has the potential to impair reproductive function and fertility in male patients. Based on its mechanism of action and genotoxic (aneugenic) and teratogenic effects seen in animal studies, alectinib can cause potential harm to a fetus.

DPMH assessment:

Due to the potential for adverse fetal and infant effects, females of reproductive potential should use effective contraception during treatment with alectinib and for one week following completion of therapy to minimize any remaining systemic exposure in a female patient. The duration on contraception use is based on multiplying the half-life (32 hours) by 6, ~8 days. In males taking drugs with a short half-life (<10 days), contraception (condom use) should be used during treatment with alectinib and for 90 days (duration of spermatogenesis cycle) after completion of therapy due to the risk of genotoxicity with alectinib use.

Alectinib can potentially cause impairment of fertility in male patients, which is a consideration since patients harboring a rearranged ALK gene/fusion protein tend to be younger, and should therefore be informed about this risk.

CONCLUSIONS

DPMH-MHT has the following recommendations for alectinib labeling:

- **Warnings and Precautions, Section 5.5**
 - Based on the increased likelihood of adverse fetal and infant effects due to alectinib's mechanism of action and embryotoxicity seen in animal reproduction studies, a subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).
- **Pregnancy, Section 8.1**
 - The "Pregnancy" subsection of alectinib labeling was formatted in the PLLR format to include "Risk Summary" and "Data" subsections.¹⁴
- **Lactation, Section 8.2**
 - The "Lactation" subsection of alectinib labeling was formatted in the PLLR¹⁵ format to include the "Risk Summary" subsection.
- **Females and Males of Reproductive Potential, Section 8.3**
 - The "Females and Males of Reproductive Potential" subsection of alectinib labeling was formatted in the PLLR format to include "Contraception" to advise females and males of reproductive potential to use effective contraception during

14 Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential.: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

15 Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

treatment and for 6 half-lives following completion of therapy (and 90 days for males based on spermatogenesis) because of the potential for adverse fetal and infant effects from exposure. This subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity¹⁶. In addition, the (b) (4) subsection was added due to data from animal studies that raised concerns about impaired human fertility in males.

- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of alectinib labeling was updated to correspond with changes made to sections 5.5, 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised subsections 5.3, 8.1, 8.2, 8.3 and 17 in labeling of alectinib for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to pregnant women. Administration of alectinib to pregnant rabbits and rats during the period of organogenesis resulted in embryotoxicity and abortion at exposures approximately 2.7-times those observed in humans with alectinib 600 mg twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 1 week following the final dose. [See Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on ALECENSA use in pregnant women. Administration of alectinib to pregnant rabbits and rats by oral gavage during the period of organogenesis resulted in embryotoxicity and abortion at exposures approximately 2.7-times those observed in humans with alectinib 600 mg twice daily [see *Data*]. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

¹⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

Animal Data

In a rabbit preliminary embryofetal study, administration of alectinib by oral gavage during the period of organogenesis resulted in abortion or complete embryo-fetal mortality at the maternally toxic dose of 27 mg/kg/day (approximately 2.9-fold the estimated human $AUC_{ss,24}$ with alectinib 600 mg BID) in three of six rabbit litters. The remaining three litters in this group had few live fetuses, decreased fetal and placental weights, and retroesophageal subclavian artery. In a rat preliminary embryofetal development study, administration of alectinib during organogenesis resulted in complete litter loss in all pregnant rats at 27 mg/kg/day (approximately 4.5-fold the estimated human $AUC_{ss,24}$ with alectinib 600 mg BID). Doses greater than or equal to 9 mg/kg/day (approximately 2.7-fold the estimated human $AUC_{ss,24}$ with alectinib 600 mg BID), resulted in maternal toxicity as well as developmental toxicities including decreased fetal weight, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae.

8.2 Lactation

Risk Summary

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breast-fed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants from alectinib, breastfeeding is not recommended during treatment with ALECENSA and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ALECENSA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 1 week after the final dose [see *Use in Specific Populations (8.1)*].

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use condoms during treatment with ALECENSA and for 3 months following the final dose. [see *Non Clinical Toxicology (13.1)*].

(b) (4)

17 PATIENT COUNSELING INFORMATION

- Embryofetal Toxicity [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)*].
 - ALECENSA can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to a fetus.

- Advise females of reproductive potential to use effective contraception during treatment with ALECENSA, and for 1 week after the last dose. Advise patients to inform their healthcare provider of a known or suspected pregnancy.
- Advise male patients with female partners of reproductive potential to use condoms during treatment with ALECENSA and for 90 days after the last dose.
- Lactation
 - Advise women not to breastfeed during treatment with ALECENSA and for 1 week after the last dose [*see Use in Specific Populations (8.2)*].

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/s/

SUCHITRA M BALAKRISHNAN
11/04/2015

TAMARA N JOHNSON
11/05/2015

LYNNE P YAO
11/06/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 2, 2015

TO: Gina Davis, Regulatory Project Manager
Erin Larkins, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #208434

APPLICANT: Hoffmann-La Roche Inc.

DRUG: Alecensa (alectinib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of ALK positive non-small cell lung cancer

CONSULTATION REQUEST DATE: July 10, 2015
INSPECTION SUMMARY GOAL DATE: November 6, 2015
DIVISION ACTION GOAL DATE: December 18, 2015
PDUFA DATE: March 2, 2016

I. BACKGROUND:

Hoffmann-La Roche, Inc., (H-LR) seeks approval to market alectinib for the treatment of patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). This intended indication is based on the efficacy and safety data from two pivotal Phase I/II, open-label, single arm, multicenter studies (NP28761 and NP28673) in patients with ALK-positive NSCLC who have progressed on previous crizotinib (Xalkori[®]) therapy.

Alectinib (also known as RO5424802 or CH5424802) is a next generation small molecule that is a highly selective and potent inhibitor of ALK and rearranged during transfection (RET) tyrosine kinase. The first generation ALK inhibitor crizotinib offers significant clinical benefit to the ALK-positive patients; however, resistance to crizotinib has been developed through a variety of mechanisms. Alectinib inhibits ALK tyrosine kinase and blocks downstream signaling pathways, such as STAT3, PI3K/AKT and MAPK, which contribute to oncogenicity. Tyrosine kinase inhibitors (TKIs) that target the kinase activity of ALK have been found to have pronounced antiproliferative and proapoptotic effects in certain ALK-positive lung cancer cells.

Study NP28761 Phase 2 component, initially planned to enroll 85 subjects. The total number of enrolled subjects was 87. Study NP28673 Phase 2 component, initially included a plan to enroll 130 subjects. The total number of enrolled subjects was 138. The primary objective for the Phase II components of these studies was to evaluate the efficacy of alectinib based on the objective response rate (ORR), based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 as per independent review committee (IRC).

Two clinical sites were chosen for inspection: Dr. Shirish Gadgeel, Detroit, MI, Site 261586 for Study NP28761 (Phase II Component) and Dr. Sai-Hong Ou, Orange, CA, Site 261589 for NP28761 (Phase II Component) and Site 259878 for Study NP28673 (Phase II Component Parts 2&3). The sponsor of these studies was also inspected.

These studies were conducted under IND 111723.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Shirish Gadgeel Wayne State University Karmanos Cancer Center 4100 John R, 4 HWCRC Detroit, MI 48201	Protocol: NP28761 Site Number: 261586 Number of Subjects: 14	August 25, 2015 – September 3, 2015	Pending Interim classification: NAI
CI#2: Sai-Hong Ou University of California Irvine 101 The City Drive South Bldg 56, Rte 8, Rm 241 Orange, CA 92868	Protocol: NP28761 Site Number: 261589 Number of Subjects: 27 Protocol: NP28673 Site Number: 259878 Number of Subjects: 5	October 2, 2015 - <u>Ongoing</u>	Pending Interim classification: To be determined upon completed of the inspection
Sponsor: Hoffmann-La Roche Inc. C/o Genentech, Inc. 1 DNA Way South San Francisco, CA 94080	Protocol: NP28761 3 Sites Covered: 261586, 261589 and 260889 Protocol: NP28673 2 Sites Covered: 259878 and 258209	September 22- 30, 2015	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: Dr. Shirish Gadgeel

(Protocol: NP28761, Phase II Component; Site Number: 261586)

- a. What was inspected:** The site screened twenty two subjects, and fifteen subjects were enrolled. The study records of all enrolled subjects were audited. At the time of this inspection there were two subjects still on study who continue to take study drug, twelve had completed the study, and one had transferred to another clinical site. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 208434, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and IRB correspondence.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be good. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoint is based on an IRC imaging review for tumor response per RECISTS1.1. Corroborating efficacy documentation reviewed at the site included records of the tumor scans sent to the IRC vendor. There was no evidence of underreporting adverse events. A Form FDA 483 was not issued.
- c. Assessment of data integrity:** The data for Dr. Gadgeel's site, associated with Study NP28761 submitted to the Agency in support of NDA 208434, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Dr. Sai-Hong Ou

Protocol: NP28761, Phase II Component; Site Number: 261589

Protocol: NP28673, Phase II Component (Parts 2&3); Site Number: 259878

- a. What was inspected:** This clinical site inspection is currently ongoing. With respect to Study NP28761, the site screened thirty six subjects and twenty eight were enrolled. The study records of 10 subjects were audited in depth. With respect to Study NP28673, the site screened six subjects and five were enrolled. The study records of 5 subjects enrolled were audited in depth. The record audit included subject medical records, subject histories, laboratory results, drug accountability, concomitant medications, sponsor correspondence, monitoring and financial disclosure compliance. The FDA investigator compared source documentation to eCRFs and data listings submitted to NDA 208434.
- b. General observations/commentary:** This clinical site inspection is currently ongoing. The primary efficacy endpoint is based on an IRC imaging review for tumor response per RECISTS1.1. Therefore, corroborating efficacy evidence was reviewed at the site that included records of the tumor scans sent to the IRC vendor. With only a few minor exceptions there was no evidence of underreporting of adverse events. There were some missed protocol-specified periodic assessments and minor documentation issues. A Form FDA 483 is expected to be issued at the conclusion of this inspection.
- c. Assessment of data integrity:** This clinical site inspection is currently ongoing. The reliability of data for Dr. Ou's site, associated with Study NP28761 and Study NP28673, submitted to the Agency in support of NDA 208434, cannot be determined until the inspection is completed.

Note: The inspection is currently ongoing but is expected to be concluded within the week. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. Sponsor: Hoffmann-La Roche Inc. c/o Genentech, Inc.

- a. What was inspected:** The inspection focused on five study sites; three for Study NP28761 and two for Study NP28673. The inspection included but was not limited to overall study conduct, test article accountability records, site monitoring, and all AEs and efficacy endpoints. The audit also included Clinical Investigator site qualification, study specific training for investigators and monitors, Form FDA 1572 and investigator agreements and assessment of monitoring procedures and monitoring plans for Studies NP28761 and NP28673.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the studies. Overall compliance with the investigational plans appeared to be good. No study sites were closed due to GCP non-compliance. Monitoring records showed studies were adequately monitored. Each site monitoring visit included coverage of informed consent, serious adverse events, protocol violations, source data verification, and discussions with site personnel including the principle investigator. There was no evidence of under-reporting of AEs/SAEs by the sponsor. There were no issues related to data validation for primary and secondary efficacy endpoints, and adverse events. Clinical investigators and sponsor monitors were adequately qualified by training, education, and/or experience. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data from this sponsor submitted to the Agency associated with Study NP28761 and Study NP28673 submitted by the sponsor to the Agency in support of NDA 208434, appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Tumor response data from the Independent Review Committee (IRC) was used to derive the primary efficacy endpoint variable for all subjects in Study NP28761 and Study NP28673. The primary efficacy outcome measures reported in the application were corroborated by the source records generated at the clinical sites. There were no trends in underreporting adverse events.

Based on the review of preliminary inspectional findings for clinical investigators Dr. Shirish Gadgeel (Site 261586; Study NP28761), and the sponsor of Study NP28761 and Study NP28673, data submitted to the Agency in support of NDA 208434, appear reliable and can be used in support of the application. The reliability of data for Dr. Sai-Hong Ou's site, associated with Study NP28761 and Study NP28673, submitted to the Agency in support of NDA 208434, cannot be determined until the inspection is completed.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

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/s/

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11/02/2015

SUSAN D THOMPSON
11/03/2015

KASSA AYALEW
11/03/2015

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	NDA 208434
Brand name	Alecensa ®
Generic Name	Alectinib
Sponsor	Hoffmann-La Roche, Inc.
Indication	Treatment of ALK positive non-small cell lung carcinoma
Dosage Form	Capsule
Drug Class	Anaplastic Lymphoma Inhibitor
Therapeutic Dosing Regimen	600 b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not achieved up to 900 mg b.i.d
Submission Number and Date	SDN 003; 06 Jul 2015
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Alectinib did not cause a large clinically relevant change in QTcF interval in the Phase I/II Study NP28761/AF-002JG. No clear dose-dependent QTc effect was observed (see Table 1). However, the safety database is difficult to interpret because of presumed disease progression. Alectinib treatment resulted in a concentration-dependent decrease from baseline in mean HR of approximately >10 bpm at the steady state. We did not find where this had been adequately described; see comments at Section 5.4.1.

The study is an open-label, phase I/II trial. Phase I of the study is a dose escalating portion to determine the recommended dose of alectinib for use in Phase II. Phase II of the study is a single arm portion to evaluate the efficacy and safety of alectinib at the dose level determined from the Phase I portion. In Phase I, a total of 47 patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib received alectinib 300 mg, alectinib 460 mg, alectinib 600 mg, alectinib 760 mg, and alectinib 900 mg (single dose on Cycle 1 Day -3 and BID dose on Days 1 to 21 of each 21-day cycle beginning from Cycle 1 Day 1). In Phase II, a total of 87 patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib received alectinib 600 mg BID. All of the 47 patients in Phase I and 84 of the 87 patients in Phase II were included in the ECG population.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Alectinib (RO5424802 300 mg to 900 mg) (FDA Analysis)

Phase	Treat	Visit	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
Phase I	RO5424802 300 mg	CYCLE 1 DAY -3	0	7	404.3 (20.4)	1.7 (15.6)	(-9.8, 13.1)
		CYCLE 2 DAY 1	4	7	415.5 (24.0)	5.2 (19.7)	(-10.9, 21.4)
	RO5424802 460 mg	CYCLE 1 DAY -3	8	7	398.6 (14.7)	2.8 (6.8)	(-3.7, 9.3)
		CYCLE 2 DAY 1	8	7	408.3 (13.0)	12.1 (8.0)	(4.5, 19.8)
	RO5424802 600 mg	CYCLE 1 DAY -3	24	13	414.9 (21.2)	1.8 (8.1)	(-2.4, 6.0)
		CYCLE 2 DAY 1	2	12	412.9 (22.1)	-2.6 (13.5)	(-9.6, 4.4)
	RO5424802 760 mg	CYCLE 1 DAY -3	24	7	398.9 (17.5)	4.6 (10.1)	(-3.7, 12.9)
		CYCLE 2 DAY 1	2	7	408.5 (14.6)	5.7 (11.2)	(-2.5, 13.9)
	RO5424802 900 mg	CYCLE 1 DAY -3	2	12	406.5 (14.1)	-0.2 (13.6)	(-9.3, 8.9)
		CYCLE 2 DAY 1	2	13	406.1 (17.7)	-0.7 (23.2)	(-14.2, 12.8)
Phase II	RO5424802 600 mg	CYCLE 1 DAY 1	0	84	408.1 (17.1)	1.9 (10.3)	(-0.1, 4.0)
		CYCLE 2 DAY 1	0	79	410.5 (19.6)	3.2 (13.7)	(0.6, 5.8)

There is no evidence of an exposure-dependent increase in Δ QTcF. The suprathreshold dose (900 mg) produces mean C_{max} values of ~1.5-fold the mean C_{max} for the therapeutic dose (600 mg). Renal or hepatic impairment or CYP3A4 inhibition is not expected to result in exposures above the suprathreshold dose.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

Because there is no clear specification of the QT documents in the consultation request, our primary reviewers only reviewed and conducted data analysis for Study NP28761/AF-002JG. We noticed the Study NP28673 report and the ECG report 106041

for the pooled analysis until our secondary review process. Because of the short timeline and the adequate information from Study NP28761, we only conducted a report review for NP28673 and 106041 and did not perform our own analyses. Based on our report review, we consider the cardiac safety findings in Report NP28673 and 106041 are consistent with the results we observed in Study NP28761 and no clinically relevant effect on QTc at the therapeutic exposure.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 PHARMACODYNAMICS

Cardiac Electrophysiology

(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

Cardiac Electrophysiology

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Alectinib is a selective and potent anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor. It is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

3.2 MARKET APPROVAL STATUS

Alectinib was approved for marketing in Japan in 2014.

3.3 PRECLINICAL INFORMATION

In the in vitro human ether-à-go-go-related gene (hERG) assay, alectinib inhibits hERG current with an IC₂₀ and an IC₅₀ of 58 and 217 ng/mL, respectively. Alectinib inhibits the current of the CaV1.2 L-type Ca²⁺ channel (IC₂₀, 98 ng/mL; IC₅₀, 222 ng/mL).

Source: IRT protocol review under IND 111723

In a preliminary telemetry study in monkeys, a slight hypotensive effect - considered due to vasodilatation induced by L-type Ca²⁺ channel inhibition - was seen at 20 and 60 mg/kg (mean C_{max}: 719 and 695 ng/mL, respectively) with no effects on electrocardiogram (ECG) or heart rate. In the GLP-compliant telemetry study in monkey, no effects on ECG, blood pressure or body temperature were observed up to 15 mg/kg per oral (mean C_{max}: 279 ng/mL).

Source: Sponsor's IB Fifth Version, September 2014

Reviewer's comments: Alectinib is a tyrosine kinase inhibitor and it inhibits hERG current with an IC₂₀ and an IC₅₀ of 58 and 217 ng/mL, respectively which is within the therapeutic exposure (the therapeutic C_{max} at steady state is ~700 ng/mL with the 600 mg b.i.d. dosing regimen). However, alectinib has very high protein binding (with %unbound < 1%) which may explain why no clinically relevant QTc prolongation was observed in the clinical study.

3.4 PREVIOUS CLINICAL EXPERIENCE

Symptomatic bradycardia can occur with ALECENSA. Cases of bradycardia ^{(b) (4)} have been reported in patients treated with ALECENSA. ^{(b) (4)} of 221 patients ^{(b) (4)} treated with ALECENSA ^{(b) (4)} 50 beats per minute [bpm].

Source: Proposed package insert.

In addition to that, the following safety events related to cardiac safety have been identified:

In Study AF-001JP, one patient had QT interval corrected using Bazett's formula (QTcB) of greater \geq 450 msec and \geq 60 msec change from baseline (407 msec to 485 msec). The case has been reviewed by a cardiovascular specialist who concluded that QT prolongation was due to the fact that the patient had a 'negative T-wave' with tumor

lesions infiltrating the cardiac muscle. Two other patients had changes from baseline in QTc between 30 and 60 msec but did not show QT prolongation over 450 msec. None of these events led to discontinuation of study drug. In Study AF-001JP, three events of bradycardia and one event of palpitations were reported out of the 58 patients who received treatment with 300 mg BID, and all were Grade 1. In Study NP28761/AF-002JG, three events of bradycardia were reported, all Grade 1 or 2. Preliminary heart rate data (based on ECG and pulse measurements) from the ongoing alectinib clinical trials show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. Similar findings have been reported with other ALK inhibitors, crizotinib and ceritinib.
Source: Sponsor's IB Fifth Version, September 2014

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of alectinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 111723. The sponsor submitted the study report 1061912 for alectinib, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A phase I/II study of the ALK inhibitor CH5424802/RO5424802 in patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib

4.2.2 Protocol Number

NP28761/AF-002JG

4.2.3 Study Dates

03 May 2012 -- 04 Aug 2014

4.2.4 Objectives

Phase I:

The primary objective for Phase I of the study was to determine the recommended Phase II dose of alectinib in patients with ALK-rearranged, locally advanced not amenable to curative therapy or metastatic NSCLC who experienced progression on crizotinib.

Secondary objectives were:

- to measure pharmacokinetic (PK) parameters of alectinib, under fasting and fed conditions, to determine whether alectinib should be administered under fasting or fed conditions in the Phase II portion
- to assess tumor response
- to evaluate the safety of alectinib
- to assess the clinical benefit of alectinib

Phase II:

The primary objective for Phase II of the study was to evaluate the efficacy of alectinib based on the ORR as per independent review committee in patients with locally advanced not amenable to curative therapy or metastatic ALKpositive NSCLC who experienced progression on crizotinib.

4.2.5 Study Description

4.2.5.1 Design

Phase I is an open-label, dose escalating study to determine the recommended dose of alectinib for use in Phase II.

Phase II is an open-label, single arm study to evaluate the efficacy and safety of alectinib at the dose level determined from the Phase I portion (600 mg BID).

4.2.5.2 Controls

There was no placebo or positive controls.

4.2.5.3 Blinding

The study was open label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 7 cohorts in Phase I (see the following table):

Alectinib 240 to 900 mg per oral (PO) single dose on Day -3 of first 21-day treatment cycle; alectinib 300 to 900 mg PO twice daily (BID) on Days 1 to 21 of each 21-day cycle. Alectinib was provided as 20 mg and 40 mg capsules in the dose escalation cohorts. Two additional PK bridging cohorts were enrolled and received alectinib 600 mg and 900 mg BID using 150 mg capsules.

	Day -3 Dose (mg)	Dose BID (mg)	Total Daily Dose (mg)
Cohort 1 (fasted)	Patients 1-3: 240 Patients 4-6: 300	300	600
Cohort 2 (fed)	460	460	920
Cohort 3	600	600	1200
Cohort 4	760	760	1520
Cohort 5	900	900	1800
Cohort 6	600*	600	1200
Cohort 7	900*	900	1800

* PK bridging cohorts: alectinib administered using 150 mg capsules. For all other cohorts, the 20 mg and 40 mg capsules were used.

Source: sponsor's clinical study report 1061912, Table 1, page 38

For analysis of safety and efficacy, patients assigned to the alectinib 600 mg and 900 mg PK bridging cohorts using the 150 mg capsules were pooled with patients who received the equivalent dose with the 20 mg and 40 mg capsules, giving five cohorts in total.

There was one arm in Phase II: Alectinib 600 mg PO BID (150 mg capsules) on Days 1 to 21 of each cycle.

4.2.6.2 Sponsor's Justification for Doses

Reviewer's Comment: The doses in this study are above the proposed therapeutic dose of 600 mg BID. Doses are acceptable given the indication.

4.2.6.3 Instructions with Regard to Meals

Doses will be administered with food. Meals are to be consumed and doses taken at the same time on each occasion.

Reviewer's Comment: Administration of drug with regards to food follows the proposed package insert. Food increases the exposure of Alectinib C_{max} : 3.31 [2.79 – 3.93], AUC_{inf} : 3.11 [2.73 – 3.55]).

4.2.6.4 ECG and PK Assessments

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Blood Sampling Schedule for Pharmacokinetic Investigation
[Phase I Portion]

Test day	Cycle 1												Day 8	Day 15
	Day -3			Day -2		Day -1		Day 1						
Time (hour)	pre-dose	Time after dose (hour)											Before morning dose	Before morning dose
		-	0.5	1	2	4	6	8	10	24	32	48	72 (Before morning dose)	-
Time range (min)	-	±5	±15	±15	±30	±30	±30	±30	±120	±120	±120	±120	±120	±120
Blood sampling for pharmacokinetics	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Test day	Cycle 2								Cycle 4		End of treatment visit
	Day 1									Day 1	
Time (hour)	pre-dose	Time after dose (hour)							Before morning dose		
		Before morning dose	0.5	1	2	4	6	8	10 (Before evening dose)	-	-
Time range (min)	±120	±5	±15	±15	±30	±30	±30	±30	±120	-	
Blood sampling for pharmacokinetics	X	X	X	X	X	X	X	X	X	X	

[Phase II Portion]

Test day	Day 1 of Cycle 1		Day 1 of Cycle 2		Day 1 of Cycle 4	End of treatment visit
Time	Before morning dose	4 hours after morning dose	Before morning dose	4 hours after morning dose	Before morning dose	-
Time range (min)	-	±30	-	±30	-	-
Blood sampling for pharmacokinetics	X	X	X	X	X	X

12-lead ECG Schedule

[Phase I Portion]

Test day	Screening	Cycle 1										
		Day -4 ¹					pre-dose	Day -3 ²				Day -2
		Time-matched baseline						Time after dose				
Time (hour)	-	Baseline ECG	2	4	6	8	-	2	4	6	8	24
Time range (min)	-14 days	-	±15	±30	±30	±30	-	±15	±30	±30	±30	±120
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X

Test day	Cycle 2					Cycle 3 and subsequent	End of treatment visit
	Day 1 ²						
	Before morning dose	Time after dose				-	-
Time (hour)	-	2	4	6	8		
Time range (min)	-	±15	±30	±30	±30	-3 days	-
12-lead ECG	X	X	X	X	X	X ³	X

[Phase II Portion]

Test day	Screening	Cycle 1				Cycle 2		Cycle 3 and subsequent	End of treatment visit
		Day -1 ³		Day 1 ⁴		Day 1 ⁴			
		Time-matched baseline		Before morning dose	Time after morning dose	Before morning dose	Time after morning dose	-	-
Time (hour)	-	Baseline ECG	Time after baseline ECG	4	4	4	4		
Time range (min)	-14 days	-	±30	-	±30	-	±30		
12-lead ECG	X	X	X	X	X	X	X	X ⁵	

(Shaded areas): ECG must be measured thrice. The results will then be sent to the central ECG laboratory.

¹: All time points should correspond to Day -3 of Cycle 1

²: The dosing time on Day -3 of Cycle 1 and on Day 1 of Cycle 2 morning expected to be performed as close to the same time as each other as possible. BP is measured at pre-dose and at 2, 4, 6, and 8 hours post-dose just prior to ECGs.

³: Both time points should correspond to Day 1 of Cycle 1

⁴: The dosing time on Day 1 of Cycle 1 and on Day 1 of Cycle 2 morning expected to be performed as close to the same time as each other as possible.

⁵: To be collected only every third cycle after Cycle 3. If an ECG shows QTc prolongation (> 470 msec.), the ECG must be repeated twice additionally to obtain values in triplicate.

Reviewer's Comment: Sampling is adequate to capture C_{max} (at median 2-4 hrs).

4.2.6.5 Baseline

The time-matched average QT/QTc values on Cycle 1 Day -4 and on Cycle 1 Day -1 were used as baselines in Phase I and Phase II, respectively.

4.2.7 ECG Collection

Standard 12-Lead ECGs were obtained while subjects were at rest.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 47 patients were enrolled and treated in Phase I. All of the 47 patients were included in the safety population, the PK population and the ECG evaluable population. The majority of patients in Phase I were white (70%) and were males (57%) with average age of 55 years, ranging from 38 years to 83 years.

A total of 87 patients were enrolled and treated in Phase II. All of the 87 patients were included in the safety population and the PK population. Of the 87 patients, 84 were included in the ECG evaluable population. The majority of patients in Phase II were white (84%) and were females (55%) with average age of 54 years, ranging from 29 years to 79 years. Patients in Phase II were relatively younger, with the large majority (82%) being younger than 65.

4.2.8.2 Statistical Analyses

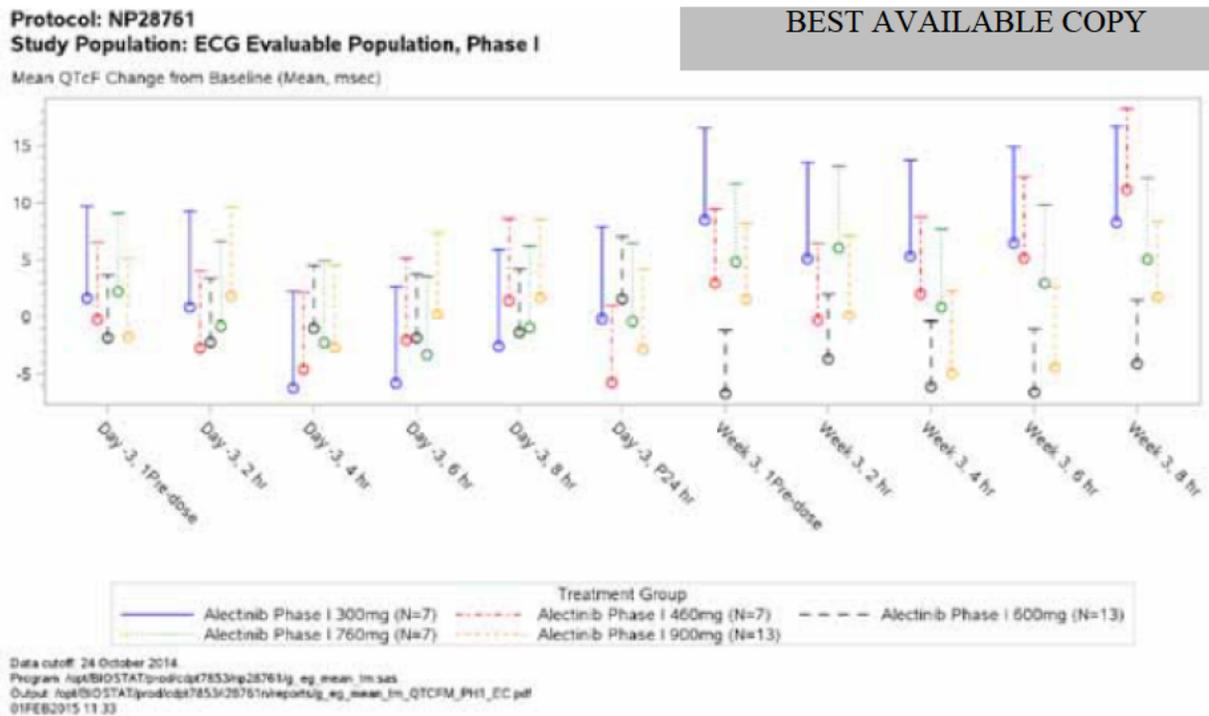
4.2.8.2.1 Primary Analysis

Alectinib did not cause a clinically relevant change in QTcF interval during Phase I. There was no apparent effect of alectinib dose on mean change from time-matched baseline in the QTcF interval. Minor changes from baseline were observed in the mean QTcF interval at pre-dose and post-dose time-points in Week 3 across all dose cohorts. The maximum post-baseline change in mean QTcF observed across all dose cohorts was 11.2 msec (8 hours post-dose, alectinib 460 mg cohort; one-sided upper 95% CI 18.3 msec).

Alectinib did not cause a clinically relevant change in QTcF interval during Phase II. Minor changes of the mean QTcF interval from time-matched baseline occurred over time during treatment with alectinib. The maximum of the mean QTcF change was 2.7 msec at Week 3 pre-dose (one-sided upper 95% CI: 5.2 msec).

The sponsor's results for primary analysis are displayed in the following figures.

Figure 1: Plot of Mean QTcF Change from Time-Matched Baseline over Time during Phase I with Upper Limit of 95% Confidence Interval



Source: sponsor's clinical study report 1061912, Figure 27, page 168

Figure 2: Plot of Mean QTcF Change from Baseline over Time with Upper Limit of 95% Confidence Interval during Phase II (ECG Evaluable Population)



Source: sponsor's clinical study report 1061912, Figure 30, page 215

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable.

4.2.8.2.3 Categorical Analysis

No patients had maximum absolute QTcF values > 500 msec during Phase I. Two patients had maximum absolute QTcF values > 450 msec while on study drug: one patient had a QTcF value > 450 msec and ≤ 480 msec (alectinib 300 mg cohort) and one patient had a QTcF value > 480 msec and ≤ 500 msec (alectinib 600 mg cohort).

No QTcF maximum increase from baseline of more than 60 msec was observed in any patient during Phase I. A total of four patients had maximum individual changes from baseline in QTcF > 30 msec and ≤ 60 msec (one patient each in alectinib 300 mg and 460 mg cohorts; two patients in alectinib 900 mg cohort).

No patients had maximum absolute QTcF values > 500 msec during Phase II. Eight patients had maximum absolute QTcF values > 450 msec while on study drug: seven patients (8%) had a QTcF value > 450 msec and ≤ 480 msec, and one patient had a QTcF value > 480 msec and ≤ 500 msec.

No QTcF maximum increase from baseline of more than 60 msec was observed in any patient during Phase II. A total of 13 patients (16%) had maximum individual changes from baseline in QTcF > 30 msec and ≤ 60 msec.

4.2.8.3 Safety Analysis

Phase I:

Overall during Phase I, 32 of the 47 patients (68%) discontinued alectinib treatment and 15 patients (32%) were still on treatment at the time of data cutoff. Of the 32 discontinued patients, 2 patients discontinued due to death and the cause of death in both cases was disease progression; 30 patients discontinued due to insufficient therapeutic response. No patients discontinued treatment prematurely due to AEs in Phase I. Of the patients who withdrew, 9 (28%) were alive in follow-up; 22 (69%) had died; and 1 (3%) was lost to follow-up.

During Phase I, all but 1 patient (46/47, 98%) experienced at least one AE. SAEs occurred in 9 patients (19%). A total of 18 patients (38%) had dose modifications or interruptions due to an AE (dose reductions 19% patients, dose interruptions 28% patients).

There were no QT interval prolongation AEs observed during Phase I. A total of 6 patients (13%) experienced AEs of sinus bradycardia during Phase I, and 1 patient experienced an AE of bradycardia. All sinus/bradycardia AEs were Grade 1 and none were reported as serious.

Phase II:

There were 12 deaths (14%) by the data cutoff date during Phase II, 11 patients (13%) died due to disease progression, and one patient (1%) died due to an SAE of hemorrhage.

All patients in Phase II experienced at least one AE. SAEs occurred in 12 patients (14%). Two patients (2%) withdrew from study drug due to liver function test abnormalities. A total of 31 patients (36%) had dose modifications or interruptions (reductions 14% patients, interruptions 29%) with the most common reason being blood CPK increased.

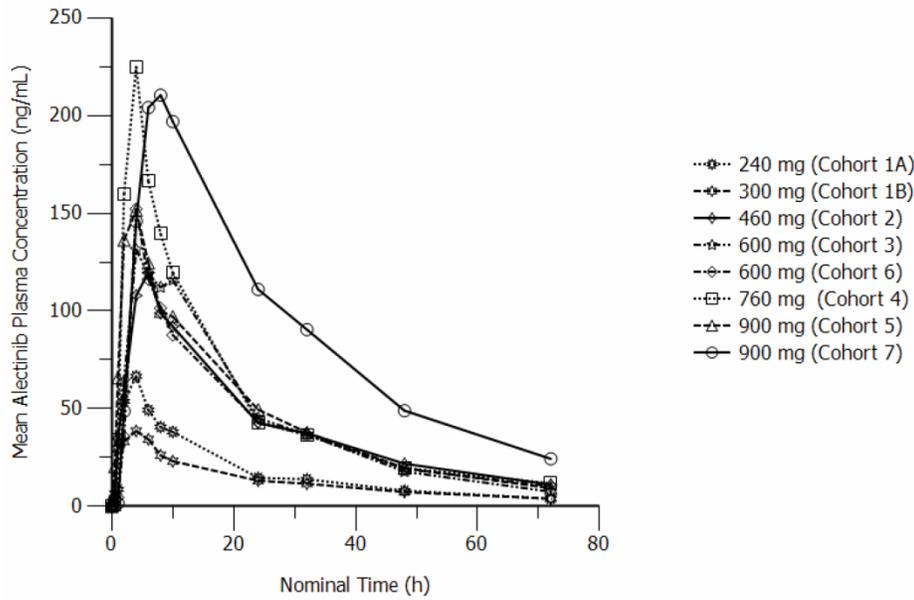
There were no QT interval prolongation AEs observed during Phase II. In total, 5 of 87 patients (6%) in Phase II experienced AEs of sinus bradycardia during the study, and 3 patients (3%) experienced AEs of bradycardia. Of these, 1 patient experienced both bradycardia and sinus bradycardia on different occasions. All sinus/bradycardia AEs were of Grade 1/2 severity, and none were reported as serious.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

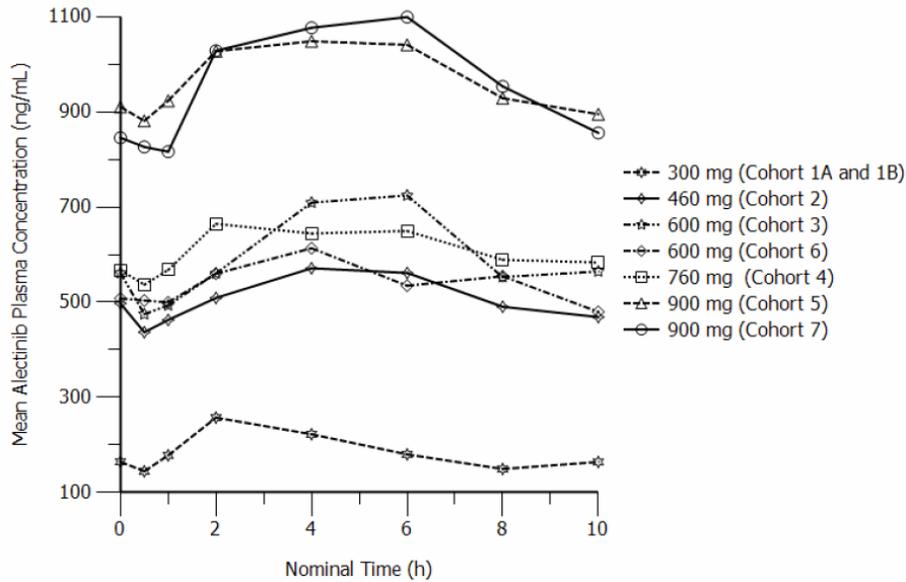
The PK results are presented in the following figures and tables. C_{max} and AUC following the highest tested dose (cohort 7 and 5: 900 mg) in the study were ~1.5-fold those with 600 mg, the intended clinical dose.

Figure 3. Mean Plasma Concentration-Time of Alectinib after Single Oral Dose Administration (Cycle 1 Day -3)



Source: Sponsor's report, figure 16

Figure 4. Mean Plasma Concentration-Time of Alectinib after Multiple Oral Dose Administration (Cycle 2 Day 1)



Source: Sponsor's report, figure 18

Table 2. Summary of Pharmacokinetic Parameters of Alectinib in Plasma after Single Oral Dose Administration (Cycle 1 Day -3)

Cohort	1A and 1B	2	3	4	5	6	7
Dose	300 mg	460 mg	600 mg ^a	760 mg	900 mg ^a	600 mg ^b	900 mg ^b
Parameter	n=6	n=7	n=5	n=5	n=7	n=6	n=4
T _{max} (h) ^a	2.21 (2.00 – 4.00)	4.00 (0.00 – 6.17)	4.17 (2.00 – 6.08)	4.00 (1.97 – 7.90)	2.10 (1.02 – 6.35)	4.39 (1.00 – 8.03)	5.02 (2.23 – 9.50)
C _{max} (ng/mL)	247 (34.6)	597 (29.7)	747 (24.6)	728 (12.9)	1060 (41.2)	607 (49.0)	1160 (29.8)
T _{last} (h)	9.41 (3.8)	8.45 (34.2)	9.74 (2.9)	9.34 (9.2)	9.95 (2.1)	9.73 (1.90)	9.69 (1.7)
C _{last} (ng/mL)	154 (40.6)	471 (35.3)	549 (27.4)	571 (24.3)	801 (54.1)	420 (63.4)	775 (53.5)
AUC _{last} (h*ng/mL)	1720 (32.4)	4200 (44.4)	5880 (19.5)	5720 (16.5)	8880 (52.1)	4620 (61.5)	9180 (32.3)
Peak to trough ratio	1.54 (14.9)	1.27 (13.7)	1.28 (6.74)	1.29 (7.66)	1.31 (20.3)	1.45 (25.4)	1.45 (12.4)
R _{acc}	6.57 (23.0) ^c	5.62 (58.5)	6.29 (33.7)	4.55 (46.1)	8.87 (78.3)	5.44 (65.0)	7.29 (64.3)

Values are reported as median (range) for T_{max}; geometric mean (geo mean CV%) for all other parameters. Patients in Cohort 1 received drug fasted, all other cohorts received drug under fed conditions

^a 20/40 mg Capsule

^b 150 mg Capsule

^c n=3 (Only patients in Cohort 1B received 300 mg on Cycle 1 Day -3 and Cycle 2 Day 1)

Source: Sponsor's report, table 36.

Table 3. Summary of Pharmacokinetic Parameters of Alectinib in Plasma after Multiple Oral Dose Administration (Cycle 2 Day 1)

Cohort	1A and 1B	2	3	4	5	6	7
Dose	300 mg	460 mg	600 mg ^a	760 mg	900 mg ^a	600 mg ^b	900 mg ^b
Parameter	n=6	n=7	n=5	n=5	n=7	n=6	n=4
T _{max} (h) ^a	2.21 (2.00 – 4.00)	4.00 (0.00 – 6.17)	4.17 (2.00 – 6.08)	4.00 (1.97 – 7.90)	2.10 (1.02 – 6.35)	4.39 (1.00 – 8.03)	5.02 (2.23 – 9.50)
C _{max} (ng/mL)	247 (34.6)	597 (29.7)	747 (24.6)	728 (12.9)	1060 (41.2)	607 (49.0)	1160 (29.8)
T _{last} (h)	9.41 (3.8)	8.45 (34.2)	9.74 (2.9)	9.34 (9.2)	9.95 (2.1)	9.73 (1.90)	9.69 (1.7)
C _{last} (ng/mL)	154 (40.6)	471 (35.3)	549 (27.4)	571 (24.3)	801 (54.1)	420 (63.4)	775 (53.5)
AUC _{last} (h*ng/mL)	1720 (32.4)	4200 (44.4)	5880 (19.5)	5720 (16.5)	8880 (52.1)	4620 (61.5)	9180 (32.3)
Peak to trough ratio	1.54 (14.9)	1.27 (13.7)	1.28 (6.74)	1.29 (7.66)	1.31 (20.3)	1.45 (25.4)	1.45 (12.4)
R _{acc}	6.57 (23.0) ^c	5.62 (58.5)	6.29 (33.7)	4.55 (46.1)	8.87 (78.3)	5.44 (65.0)	7.29 (64.3)

Values are reported as median (range) for T_{max}; geometric mean (geo mean CV%) for all other parameters. Patients in Cohort 1 received drug fasted, all other cohorts received drug under fed conditions

^a 20/40 mg Capsule

^b 150 mg Capsule

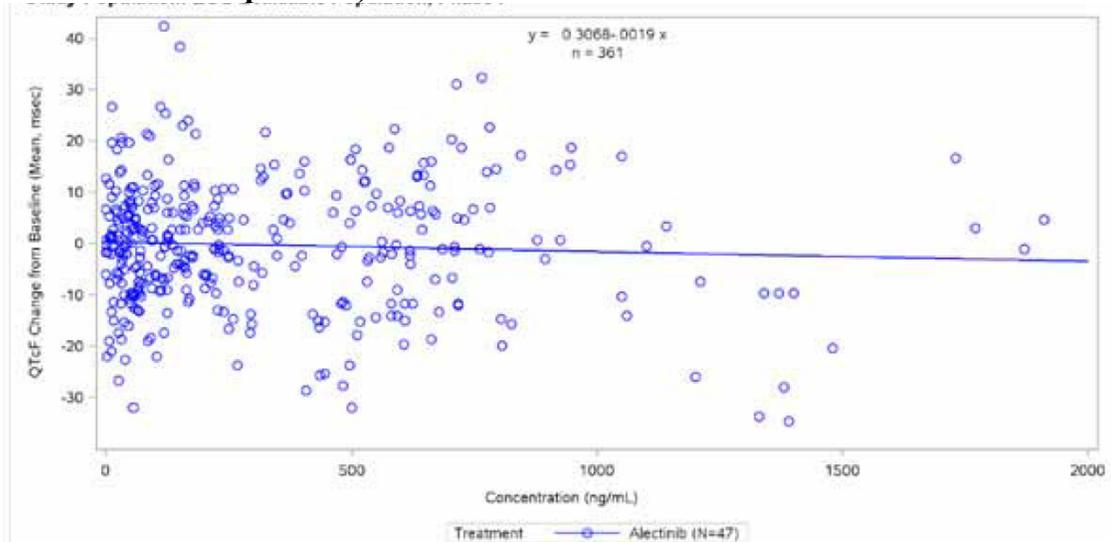
^c n=3 (Only patients in Cohort 1B received 300 mg on Cycle 1 Day -3 and Cycle 2 Day 1)

Source: Sponsor's report, table 38.

4.2.8.4.2 Exposure-Response Analysis

Results of sponsor's exposure-response analysis using simple linear regression are shown below (Figure 5). Applicant estimates a non-significant negative slope and concludes that no correlation is found between exposure and QTcF.

Figure 5. Scatter Plot of Individual QTcF Change from Time-Matched Baseline versus Alectinib Concentration in Plasma at all Time Points during Phase I (ECG Evaluable Population)



Source: Sponsor's report, figure 28.

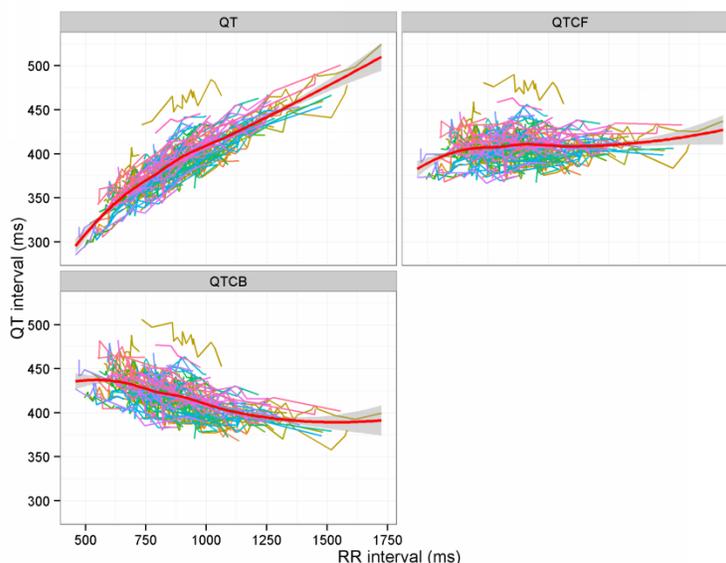
Reviewer's Analysis: A plot of ΔQTc vs. drug concentrations is presented in Figure 8.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 6. This statistical reviewer used QTcF for the primary statistical analysis.

Figure 6: QT, QTcB, and QTcF, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Alectinib (RO5424802)

The primary endpoint is the mean change from baseline in QTcF (Δ QTcF). The descriptive statistics of Δ QTcF from Cycle 1 and Cycle 2 are listed in the following tables.

The largest mean change from baseline in QTcF (Δ QTcF) was 12.1 ms with a 90% CI of 4.5 ms to 19.8 ms in the 460 mg group. The largest upper bound of the 2-sided 90% CI for the mean change from baseline in QTcF (Δ QTcF) was slightly above 20 ms (21.4 ms) in the 300 mg group, but the value is associated with uncertainties that might be caused by small sample size and large variation.

Table 4: Analysis Results of Δ QTcF for Treatment Group = Alectinib 300 mg and Alectinib 460 mg in Phase I

Phase	Treat	Visit	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)			
Phase I	RO5424802 300 mg	CYCLE 1 DAY -3	0	7	404.3 (20.4)	1.7 (15.6)	(-9.8, 13.1)			
			2	7	409.1 (18.9)	0.2 (12.0)	(-9.7, 10.1)			
			4	7	404.0 (19.3)	-5.6 (16.9)	(-19.5, 8.3)			
			6	7	401.6 (20.7)	-5.7 (15.5)	(-18.4, 7.0)			
			8	7	403.8 (15.5)	-3.1 (12.5)	(-13.3, 7.2)			
			24	7	402.5 (17.3)	-0.1 (13.1)	(-9.8, 9.5)			
			0	7	411.1 (19.5)	8.5 (10.4)	(0.8, 16.2)			
			CYCLE 2 DAY 1	2	7	413.3 (18.8)	5.6 (18.5)	(-9.6, 20.8)		
				4	7	415.5 (24.0)	5.2 (19.7)	(-10.9, 21.4)		
				6	7	413.9 (17.5)	7.6 (11.8)	(-2.2, 17.3)		
				8	7	414.6 (17.0)	8.6 (7.2)	(2.7, 14.4)		
				RO5424802 460 mg	CYCLE 1 DAY -3	0	7	394.7 (16.2)	-0.2 (9.7)	(-8.1, 7.8)
				2		7	400.0 (17.0)	-1.4 (12.8)	(-10.8, 8.0)	
				4		7	401.0 (11.8)	-1.2 (11.9)	(-10.0, 7.5)	
6	7	397.9 (10.9)	-1.5 (6.9)	(-8.1, 5.1)						
8	7	398.6 (14.7)	2.8 (6.8)	(-3.7, 9.3)						
24	7	387.0 (11.7)	-5.3 (9.0)	(-12.7, 2.1)						
0	7	397.9 (16.6)	3.0 (15.9)	(-8.7, 14.7)						
			2	7	402.4 (14.6)	1.0 (14.6)	(-9.7, 11.8)			
			4	7	407.6 (14.3)	5.4 (10.5)	(-2.3, 13.1)			
			6	7	405.0 (9.5)	5.9 (5.9)	(0.2, 11.5)			
			8	7	408.3 (13.0)	12.1 (8.0)	(4.5, 19.8)			

Table 5: Analysis Results of Δ QTcF for Treatment Group = Alectinib 600 mg and Alectinib 760 mg in Phase I

Phase	Treat	Visit	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)	
Phase I	RO5424802 600 mg	CYCLE 1 DAY -3	0	13	407.8 (20.6)	-2.6 (8.4)	(-6.9, 1.8)	
			2	13	411.2 (25.0)	-0.9 (10.2)	(-6.2, 4.4)	
			4	13	414.9 (22.7)	-0.5 (6.2)	(-3.6, 2.6)	
			6	13	415.1 (22.7)	0.1 (11.4)	(-5.8, 6.0)	
			8	13	411.1 (23.5)	-1.0 (12.7)	(-7.3, 5.3)	
			24	13	414.9 (21.2)	1.8 (8.1)	(-2.4, 6.0)	
		CYCLE 2 DAY 1	0	11	406.2 (21.5)	-5.9 (16.9)	(-15.1, 3.3)	
	2		12	412.9 (22.1)	-2.6 (13.5)	(-9.6, 4.4)		
	4		12	412.5 (23.8)	-6.3 (12.3)	(-13.0, 0.4)		
	6		12	413.3 (24.7)	-6.4 (13.4)	(-13.3, 0.5)		
	8		12	411.5 (25.4)	-3.9 (12.9)	(-10.6, 2.8)		
			RO5424802 760 mg	CYCLE 1 DAY -3	0	7	401.5 (9.4)	3.8 (7.3)
	2	7			400.9 (16.4)	-0.8 (8.7)	(-7.9, 6.3)	
	4	7			403.5 (14.0)	-2.7 (4.1)	(-6.1, 0.7)	
6	7	400.8 (11.2)			-3.3 (9.4)	(-10.2, 3.6)		
8	7	401.2 (12.5)			0.3 (5.4)	(-4.1, 4.7)		
24	7	398.9 (17.5)			4.6 (10.1)	(-3.7, 12.9)		
	CYCLE 2 DAY 1	0			7	404.1 (13.8)	2.6 (9.6)	(-5.4, 10.5)
2		7			408.5 (14.6)	5.7 (11.2)	(-2.5, 13.9)	
4		7	407.4 (16.6)	0.8 (10.0)	(-6.5, 8.2)			
6		7	407.1 (13.8)	3.0 (11.0)	(-5.1, 11.1)			
			8	7	407.2 (18.8)	4.4 (11.2)	(-4.8, 13.6)	

Table 6: Analysis Results of Δ QTcF for Alectinib 900 mg in Phase I and Alectinib 600 mg in Phase II

Phase	Treat	Visit	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
Phase I	RO5424802 900 mg	CYCLE 1 DAY -3	0	13	404.8 (13.0)	-2.3 (6.8)	(-6.0, 1.4)
			2	12	406.5 (14.1)	-0.2 (13.6)	(-9.3, 8.9)
			4	13	409.1 (12.6)	-4.4 (13.3)	(-12.7, 3.9)
			6	13	408.1 (16.4)	0.7 (9.9)	(-5.0, 6.4)
			8	13	410.3 (12.0)	1.6 (7.5)	(-2.5, 5.7)
			24	12	405.9 (9.9)	-2.5 (11.2)	(-8.9, 4.0)
		CYCLE 2 DAY 1	0	12	410.0 (18.6)	0.7 (18.9)	(-9.6, 11.0)
			2	13	406.1 (17.7)	-0.7 (23.2)	(-14.2, 12.8)
			4	13	406.8 (16.7)	-5.5 (16.1)	(-15.5, 4.5)
			6	13	405.4 (15.3)	-2.0 (13.2)	(-9.2, 5.2)
Phase II	RO5424802 600 mg	CYCLE 1 DAY 1	0	84	408.1 (17.1)	1.9 (10.3)	(-0.1, 4.0)
			4	81	409.6 (20.1)	0.1 (10.8)	(-2.0, 2.2)
		CYCLE 2 DAY 1	0	79	410.5 (19.6)	3.2 (13.7)	(0.6, 5.8)
			4	77	409.8 (19.0)	1.2 (14.2)	(-1.7, 4.0)

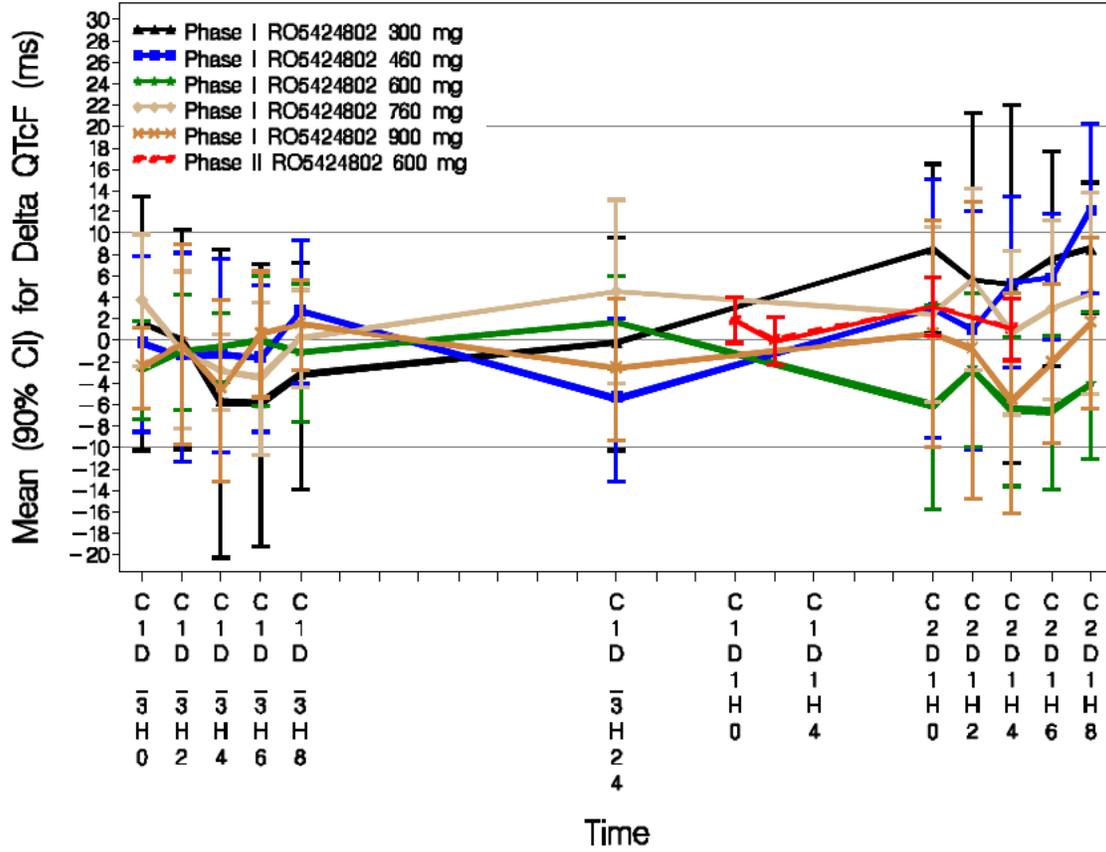
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of Δ QTcF Over Time

The following figure displays the time profile of Δ QTcF for different treatment groups.

Figure 7: Mean and 90% CI Δ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 7 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms.

Table 7: Categorical Analysis for QTcF (Data from Cycle 1 & Cycle 2)

Phase	Treatment Group	Total N		QTcF ≤ 450 ms		450 < QTcF ≤ 480 ms		480 < QTcF ≤ 500 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Phase I	Baseline	47	211	45 (95.7%)	205 (97.2%)	1 (2.1%)	2 (0.9%)	1 (2.1%)	4 (1.9%)
	RO5424802 300 mg	7	77	6 (85.7%)	76 (98.7%)	1 (14.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
	RO5424802 460 mg	7	76	7 (100%)	76 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RO5424802 600 mg	13	134	12 (92.3%)	123 (91.8%)	0 (0.0%)	10 (7.5%)	1 (7.7%)	1 (0.7%)
	RO5424802 760 mg	7	75	7 (100%)	75 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	RO5424802 900 mg	12	123	12 (100%)	123 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Phase II	Baseline	78	148	77 (98.7%)	146 (98.6%)	1 (1.3%)	2 (1.4%)	0 (0.0%)	0 (0.0%)
	RO5424802 600 mg	83	305	79 (95.2%)	300 (98.4%)	4 (4.8%)	5 (1.6%)	0 (0.0%)	0 (0.0%)

Table 8 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 8: Categorical Analysis of Δ QTcF (Data from Cycle 1 and Cycle 2)

Phase	Treatment Group	Total N		Δ QTcF \leq 30 ms		30 $<$ Δ QTcF \leq 60 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Phase I	RO5424802 300 mg	7	69	6 (85.7%)	67 (97.1%)	1 (14.3%)	2 (2.9%)
	RO5424802 460 mg	7	67	7 (100%)	67 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 600 mg	13	132	13 (100%)	132 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 760 mg	7	70	7 (100%)	70 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 900 mg	12	112	10 (83.3%)	110 (98.2%)	2 (16.7%)	2 (1.8%)
Phase II	RO5424802 600 mg	81	285	79 (97.5%)	283 (99.3%)	2 (2.5%)	2 (0.7%)

5.2.2 HR Analysis

The primary endpoint is the mean change from baseline in HR (Δ HR). The descriptive statistics of Δ HR from Cycle 1 and Cycle 2 are listed in Table 9, Table 10, and Table 11.

An HR lowering effect was observed as early as 6 to 8 hours post dose on Day -3, for all cohorts in Phase I except the 300 mg group. Larger HR lowering effect was observed in Cycle 2, and the largest mean change from baseline in HR (Δ HR) on Cycle 2 Day 1 was -20.5 bpm in the 900 mg cohort.

In Phase II, the largest mean change from baseline in HR (Δ HR) by Cycle 2 Day 1 was -15.0 bpm.

The outlier analysis results for HR are presented in Table 12.

Table 9: Analysis Results of Δ HR for Treatment Group = Alectinib 300 mg and Alectinib 460 mg in Phase I

Phase	Treat	Visit	Time	N	HR (bpm) (SD)	Δ HR (bpm) (SD)	Δ HR 90% CI (bpm)		
Phase I	RO5424802 300 mg	CYCLE 1 DAY -3	0	7	70.7 (21.4)	-6.0 (6.2)	(-10.5, -1.5)		
			2	7	71.5 (19.6)	3.7 (5.8)	(-1.1, 8.4)		
			4	7	74.3 (17.9)	2.0 (10.6)	(-6.7, 10.8)		
			6	7	72.2 (17.4)	0.3 (9.8)	(-7.8, 8.4)		
			8	7	74.0 (17.5)	2.1 (10.4)	(-6.4, 10.6)		
			24	7	74.3 (17.1)	-2.4 (8.8)	(-8.9, 4.0)		
			CYCLE 2 DAY 1	0	7	62.5 (21.4)	-14.3 (7.3)	(-19.6, -8.9)	
			2	7	62.9 (18.0)	-6.5 (5.7)	(-11.2, -1.8)		
			4	7	65.6 (20.3)	-6.9 (10.7)	(-15.7, 2.0)		
			6	7	64.1 (19.9)	-8.0 (10.1)	(-16.3, 0.3)		
			8	7	65.1 (17.7)	-8.2 (5.9)	(-13.1, -3.3)		
		RO5424802 460 mg	CYCLE 1 DAY -3	0	7	75.2 (22.4)	-0.9 (10.4)	(-9.4, 7.6)	
					2	7	74.6 (17.4)	2.2 (7.5)	(-3.3, 7.7)
					4	7	72.2 (16.4)	1.5 (8.5)	(-4.7, 7.7)
				6	7	70.7 (17.7)	-2.5 (5.2)	(-7.5, 2.4)	
				8	7	69.7 (16.3)	-5.8 (7.5)	(-12.9, 1.3)	
				24	7	77.2 (20.8)	1.2 (10.9)	(-6.8, 9.2)	
				CYCLE 2 DAY 1	0	7	61.5 (10.1)	-14.4 (12.4)	(-23.6, -5.3)
			2	7	60.3 (9.7)	-12.1 (17.4)	(-24.9, 0.7)		
			4	7	62.5 (7.6)	-8.1 (14.1)	(-18.5, 2.2)		
			6	7	63.0 (9.7)	-8.3 (17.3)	(-24.8, 8.3)		
			8	7	61.8 (9.7)	-10.5 (18.0)	(-27.7, 6.6)		

Table 10: Analysis Results of Δ HR for Treatment Group = Alectinib 600 mg and Alectinib 760 mg in Phase I

Phase	Treat	Visit	Time	N	HR (bpm) (SD)	Δ HR (bpm) (SD)	Δ HR 90% CI (bpm)
Phase I	RO5424802 600 mg	CYCLE 1 DAY -3	0	13	79.0 (14.1)	3.2 (9.3)	(-1.4, 7.8)
			2	13	76.7 (13.5)	3.5 (6.6)	(0.2, 6.8)
			4	13	77.8 (13.9)	2.0 (8.2)	(-2.1, 6.0)
			6	13	76.8 (13.3)	0.1 (8.2)	(-3.9, 4.2)
			8	13	74.9 (15.4)	-1.4 (9.7)	(-6.2, 3.4)
			24	13	77.8 (17.1)	2.0 (12.5)	(-4.2, 8.2)
			0	11	61.5 (7.6)	-11.4 (10.1)	(-16.9, -5.9)
	RO5424802 760 mg	CYCLE 2 DAY 1	2	12	61.5 (6.2)	-9.9 (7.2)	(-13.6, -6.2)
			4	12	61.2 (3.9)	-12.9 (6.0)	(-16.0, -9.8)
			6	12	61.3 (6.6)	-13.7 (5.9)	(-16.8, -10.7)
			8	12	59.2 (6.7)	-15.1 (6.9)	(-18.7, -11.5)
			0	7	78.6 (10.2)	0.9 (8.0)	(-5.0, 6.7)
			2	7	72.2 (6.5)	-1.8 (2.9)	(-3.9, 0.4)
			4	7	72.7 (5.7)	-3.0 (2.8)	(-5.1, -1.0)
RO5424802 760 mg	CYCLE 1 DAY -3	6	7	69.3 (7.6)	-9.5 (7.9)	(-15.3, -3.7)	
		8	7	66.6 (5.7)	-6.2 (8.3)	(-12.3, -0.1)	
		24	7	71.2 (7.5)	-6.5 (9.0)	(-13.2, 0.1)	
		0	7	62.7 (8.0)	-15.0 (14.5)	(-25.7, -4.4)	
		2	7	61.8 (7.6)	-12.2 (8.3)	(-18.3, -6.1)	
		4	7	60.3 (8.1)	-15.3 (7.6)	(-20.9, -9.8)	
		6	7	63.7 (10.9)	-15.1 (8.3)	(-21.3, -9.0)	
		8	7	61.3 (11.6)	-11.5 (6.0)	(-16.0, -7.1)	

Table 11: Analysis Results of Δ HR for Alectinib 900 mg in Phase I and Alectinib 600 mg in Phase II

Phase	Treat	Visit	Time	N	HR (bpm) (SD)	Δ HR (bpm) (SD)	Δ HR 90% CI (bpm)	
Phase I	RO5424802 900 mg	CYCLE 1 DAY -3	0	13	82.0 (16.9)	-0.4 (4.4)	(-2.6, 1.8)	
			2	12	81.8 (16.6)	4.2 (8.1)	(0.1, 8.4)	
			4	13	78.6 (14.6)	0.7 (6.9)	(-2.8, 4.3)	
			6	13	77.7 (12.5)	-4.9 (8.7)	(-9.2, -0.6)	
			8	13	75.9 (13.3)	-4.8 (10.9)	(-10.2, 0.6)	
				24	12	81.7 (15.3)	0.9 (7.6)	(-3.0, 4.8)
			CYCLE 2 DAY 1	0	12	62.3 (12.7)	-20.5 (13.9)	(-27.7, -13.3)
				2	13	64.5 (14.6)	-12.2 (9.7)	(-17.0, -7.4)
				4	13	65.2 (13.0)	-10.7 (9.8)	(-15.8, -5.6)
				6	13	65.0 (11.8)	-17.6 (9.5)	(-22.3, -12.9)
	8	13		63.7 (12.5)	-17.0 (12.1)	(-23.0, -11.0)		
Phase II	RO5424802 600 mg	CYCLE 1 DAY 1	0	84	76.9 (17.7)	-2.0 (8.7)	(-3.6, -0.4)	
			4	81	79.0 (16.1)	-1.7 (8.3)	(-3.3, -0.2)	
			CYCLE 2 DAY 1	0	79	63.8 (14.4)	-15.0 (13.0)	(-17.5, -12.6)
				4	77	67.2 (14.5)	-12.3 (11.4)	(-14.6, -10.1)

Table 12: Categorical Analysis for HR (Data from Cycle 1 and Cycle 2)

		Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Phase	Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Phase I	Baseline	47	40 (85.1%)	7 (14.9%)	46 (97.9%)	1 (2.1%)
	RO5424802 300 mg	7	7 (100%)	0 (0.0%)	5 (71.4%)	2 (28.6%)
	RO5424802 460 mg	7	6 (85.7%)	1 (14.3%)	7 (100%)	0 (0.0%)
	RO5424802 600 mg	13	12 (92.3%)	1 (7.7%)	13 (100%)	0 (0.0%)
	RO5424802 760 mg	7	7 (100%)	0 (0.0%)	6 (85.7%)	1 (14.3%)
	RO5424802 900 mg	13	11 (84.6%)	2 (15.4%)	11 (84.6%)	2 (15.4%)
Phase II	Baseline	81	67 (82.7%)	14 (17.3%)	81 (100%)	0 (0.0%)
	RO5424802 600 mg	84	71 (84.5%)	13 (15.5%)	79 (94.0%)	5 (6.0%)

5.2.3 PR Analysis

The primary endpoint is the mean change from baseline in PR (Δ PR). The point estimates and the 90% CIs corresponding to the largest upper bounds for Δ PR are listed in the following Table 13 (tables at time point level are omitted).

The largest mean change from baseline in PR (Δ PR) by Cycle 2 Day 1 was 14.9 ms and 6.9 ms during Phase I and Phase II, respectively.

The outlier analysis results for PR are presented in Table 14.

Table 13: Analysis Results of Δ PR

Phase	Treat	Visit	Time	N	PR (ms) (SD)	Δ PR (ms) (SD)	Δ PR 90% CI (ms)
Phase I	RO5424802 300 mg	CYCLE 1 DAY -3	8	7	159.8 (18.3)	0.8 (11.9)	(-8.9, 10.6)
		CYCLE 2 DAY 1	6	7	168.6 (21.0)	8.3 (14.6)	(-3.7, 20.3)
	RO5424802 460 mg	CYCLE 1 DAY -3	6	7	160.1 (18.1)	4.1 (11.8)	(-7.2, 15.4)
		CYCLE 2 DAY 1	8	7	173.2 (12.1)	14.9 (14.0)	(1.6, 28.2)
	RO5424802 600 mg	CYCLE 1 DAY -3	8	13	169.2 (26.6)	3.2 (7.8)	(-0.6, 7.0)
		CYCLE 2 DAY 1	6	12	179.7 (27.8)	10.4 (8.9)	(5.8, 15.0)
	RO5424802 760 mg	CYCLE 1 DAY -3	2	7	161.0 (19.2)	7.9 (11.5)	(-0.5, 16.3)
		CYCLE 2 DAY 1	4	7	160.3 (22.1)	9.0 (4.9)	(5.4, 12.7)
	RO5424802 900 mg	CYCLE 1 DAY -3	6	13	152.6 (18.2)	5.5 (10.4)	(0.4, 10.6)
		CYCLE 2 DAY 1	2	13	161.5 (24.9)	11.9 (19.4)	(2.3, 21.5)
Phase II	RO5424802 600 mg	CYCLE 1 DAY 1	4	81	153.4 (18.3)	1.1 (8.7)	(-0.6, 2.7)
		CYCLE 2 DAY 1	0	79	158.0 (19.7)	6.9 (11.3)	(4.8, 9.0)

Table 14: Categorical Analysis for PR (Data from Cycle 1 and Cycle 2)

Phase	Treatment Group	Total N		PR≤200 ms		PR>200 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Phase I	Baseline	47	225	44 (93.6%)	218 (96.9%)	3 (6.4%)	7 (3.1%)
	RO5424802 300 mg	7	77	5 (71.4%)	72 (93.5%)	2 (28.6%)	5 (6.5%)
	RO5424802 460 mg	7	77	6 (85.7%)	75 (97.4%)	1 (14.3%)	2 (2.6%)
	RO5424802 600 mg	13	137	10 (76.9%)	108 (78.8%)	3 (23.1%)	29 (21.2%)
	RO5424802 760 mg	7	77	7 (100%)	77 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 900 mg	13	140	12 (92.3%)	137 (97.9%)	1 (7.7%)	3 (2.1%)
Phase II	Baseline	81	157	80 (98.8%)	156 (99.4%)	1 (1.2%)	1 (0.6%)
	RO5424802 600 mg	84	321	82 (97.6%)	317 (98.8%)	2 (2.4%)	4 (1.2%)

5.2.4 QRS Analysis

The primary endpoint is the mean change from baseline in QRS (Δ QRS). The point estimates and the 90% CIs corresponding to the largest upper bounds for Δ PR are listed in Table 15 (tables at time point level are omitted).

The largest mean change from baseline in QRS (Δ QRS) by Cycle 2 Day 1 was 4.6 ms and 1.9 ms during Phase I and Phase II, respectively.

The outlier analysis results for QRS are presented in Table 16.

Table 15: Analysis Results of Δ QRS

Phase	Treat	Visit	Time	N	QRS (ms) (SD)	ΔQRS (ms) (SD)	ΔQRS 90% CI (ms)
Phase I	RO5424802 300 mg	CYCLE 1 DAY -3	24	7	90.5 (10.9)	4.0 (6.9)	(-1.1, 9.1)
		CYCLE 2 DAY 1	0	7	87.6 (10.9)	1.1 (9.1)	(-5.6, 7.8)
	RO5424802 460 mg	CYCLE 1 DAY -3	4	7	90.0 (9.8)	3.8 (6.6)	(-1.1, 8.6)
		CYCLE 2 DAY 1	8	7	87.9 (6.5)	4.0 (7.6)	(-3.3, 11.3)
	RO5424802 600 mg	CYCLE 1 DAY -3	8	13	88.7 (6.7)	1.1 (7.1)	(-2.4, 4.6)
		CYCLE 2 DAY 1	4	12	90.9 (7.5)	2.9 (6.6)	(-0.5, 6.3)
	RO5424802 760 mg	CYCLE 1 DAY -3	0	7	87.3 (6.8)	4.6 (3.9)	(1.8, 7.5)
		CYCLE 2 DAY 1	0	7	87.2 (3.9)	4.5 (6.5)	(-0.2, 9.3)
	RO5424802 900 mg	CYCLE 1 DAY -3	8	13	87.7 (12.0)	2.3 (6.8)	(-1.1, 5.6)
		CYCLE 2 DAY 1	8	13	89.4 (13.4)	4.0 (6.4)	(0.8, 7.1)
Phase II	RO5424802 600 mg	CYCLE 1 DAY 1	4	81	87.6 (8.9)	-0.1 (5.9)	(-1.2, 1.0)
		CYCLE 2 DAY 1	0	79	89.0 (7.8)	1.9 (6.5)	(0.7, 3.1)

Table 16: Categorical Analysis for QRS (Data from Cycle 1 and Cycle 2)

Phase	Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
		Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Phase I	Baseline	47	225	46 (97.9%)	220 (97.8%)	1 (2.1%)	5 (2.2%)
	RO5424802 300 mg	7	77	7 (100%)	77 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 460 mg	7	77	7 (100%)	77 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 600 mg	13	137	13 (100%)	137 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 760 mg	7	77	7 (100%)	77 (100%)	0 (0.0%)	0 (0.0%)
	RO5424802 900 mg	13	140	12 (92.3%)	130 (92.9%)	1 (7.7%)	10 (7.1%)
Phase II	Baseline	81	157	79 (97.5%)	153 (97.5%)	2 (2.5%)	4 (2.5%)
	RO5424802 600 mg	84	321	81 (96.4%)	315 (98.1%)	3 (3.6%)	6 (1.9%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF and alectinib concentrations is visualized in Figure 8 with no evident exposure-response relationship (similar exposure-response analysis was also performed for M4 with no evident relationship). However, a significant relationship between alectinib concentration and decrease from baseline in mean HR was observed (Figure 9).

Figure 8: Δ QTcF vs. alectinib plasma concentration

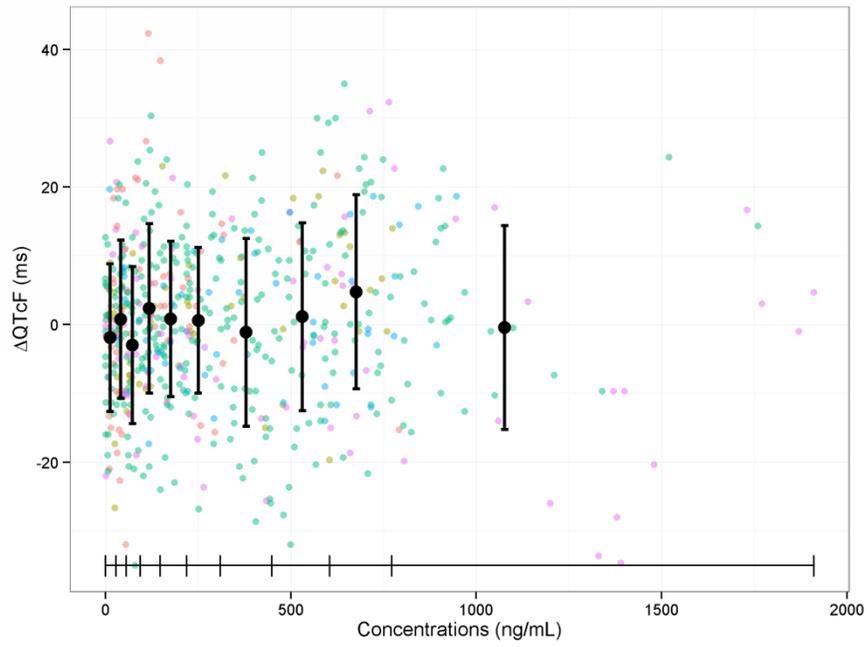
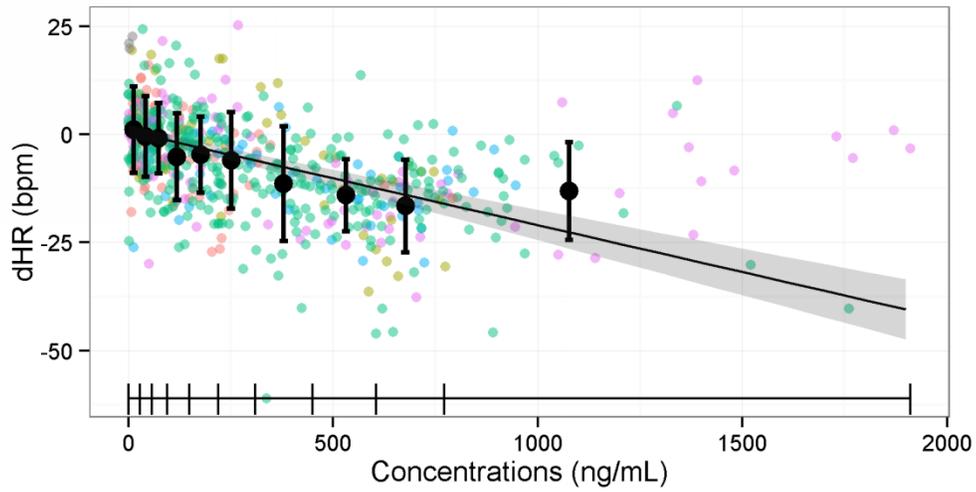


Figure 9: Δ HR vs. alectinib plasma concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Deaths in this program have been attributed to underlying disease, but the bradycardia is concerning. We did not see much explanation in the Investigator's Brochure whether this was seen and evaluated nonclinically. In the clinical development program, it would also be useful to know if humans drop their blood pressure. Is the myocardial depression reversible?

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Neither PR nor QRS was affected to any clinically significant extent.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	RO5424802 currently being evaluated at doses up to 900 mg BID in ongoing dose escalation for determination of the recommended phase II dose selection; expected therapeutic dose: 600 to 900 mg BID	
Maximum Tolerated Dose	Not achieved in clinical studies; doses up to 900 mg BID well tolerated	
NOAEL	No NOAELs established in GLP toxicology studies	
Principal Adverse Events	Adverse events occurring with an incidence $\geq 20\%$: dysgeusia, rash, constipation, aspartate aminotransferase (AST) increased, blood creatinine increased, alanine aminotransferase (ALT) increased.	
Maximum Dose Tested	Single dose	900 mg
	Multiple dose	900 mg BID x 21 days
Exposures Achieved at Maximum Tested Dose	Single dose	Mean (%CV) C_{max} = 186 ng/mL (64.7%) at 900 mg (n = 7) Mean (%CV) $AUC_{0-\infty}$ = 3740 ng.h/mL (61.6%) at 900 mg (n = 7)
	Multiple dose	Mean (%CV) C_{max} = 1140 ng/mL (39.4%) at 900 mg (n = 7) Mean (%CV) AUC_{0-10} = 9840 ng.h/mL (46.9%) at 900 mg (n = 7)
Range of Linear PK	Steady-state PK appears dose proportional from 20-300 mg BID under fasted conditions in Japanese patients. In US patients receiving higher doses steady-state PK appears to increase less than dose proportionally from 460-900 mg BID under fed conditions based on limited preliminary data	
Accumulation at steady-state (based on AUC)	600 mg BID in US patients: Mean (%CV) = 6.35 (35.2%) 760 mg BID in US patients: Mean (%CV) = 4.69 (44.8%) 900 mg BID in US patients: Mean (%CV) = 11.1 (72.5%)	
Metabolites	RO5468924 (M4), the major active metabolite of RO5424802	
Absorption	Absolute/Relative BA	No absolute or relative BA evaluated yet
	T_{max} (h)	Median (range) = 2.0h (1.0-6.0) at 900 mg multiple dose (n = 7) for RO5424802 Median (range) = 4.0h (0.5-8.0) at 300 mg multiple dose (n=6) for RO5468924 (M4)
Distribution	$V_{d_{ss}}/F$	Mean (%CV) = 2530 L (55.4%) at 900 mg BID (n=7)
	% unbound	Mean (%CV) = < 1%
Elimination	Route	No human mass balance data available yet. In rats, 95.7% and 0.5% of the administered radioactivity was recovered in feces and urine, respectively.
	Terminal $t_{1/2}$	Mean (%CV) = 21.0h (14.6%) at 900 mg single dose (n = 7) for RO5424802 Mean (%CV) = 23.5h (23.3%) at 300 mg single dose (n=6) for RO5468924 (M4)

	CL _{ss} /F	Mean (%CV) = 94.9 L/hr (48.2%) at 900 mg BID (n=7)
Intrinsic Factors	Age	To be evaluated using popPK
	Gender	To be evaluated using popPK
	Race	Median exposure in Japanese ALK+ NSCLC patients appears to be approximately 2-fold higher at 300 mg BID than in US ALK+ NSCLC patients based on cross study comparison of interim data.
	Hepatic and Renal impairment	No data is available in hepatic or renal impairment.
Extrinsic Factors	Drug interactions	RO5424802 is predominately metabolized by CYP3A. RO5424802 has shown weak time-dependent inhibition of CYP3A and small induction potential for CYP3A, CYP1A2, and CYP2B6 <i>in vitro</i> . RO5424802 is an inhibitor of P-gp and BCRP transporters <i>in vitro</i> . RO5424802 solubility is pH dependent with decreasing solubility at increasing pH. No drug-drug interaction studies have been formally conducted yet.
	Food effects	A parallel group comparison of RO5424802 administered under fed conditions delayed T _{max} by approximately 2-4 hours and increased RO5424802 exposure (AUC ₀₋₇₂ and C _{max}) by approximately 1.8-2.4 fold relative to administration under fasting conditions following single doses. At steady-state, no substantial food effect was observed on RO5424802 exposure (AUC ₀₋₁₀ and C _{max}) based on parallel group comparison. It is important to note that fasting times were different between single dose and multiple dose conditions which may have affected assessments. Meal content was not controlled in the study.
Expected High Clinical Exposure Scenarios	Median exposure in Japanese ALK+ NSCLC patients appears to be approximately 2-fold higher at 300 mg BID than in US ALK+ NSCLC patients based on cross study comparison of interim data. As RO5424802 is predominately metabolized by CYP3A, potent CYP3A inhibitors may have the potential to increase RO5424802 exposure. No formal drug-drug interaction data with a potent CYP3A inhibitor (i.e. ketoconazole) is available yet. As RO5424802 is predominately metabolized in the liver by CYP3A; hepatic impairment may have the potential to alter RO5424802 exposure.	

The table below was submitted to the Agency in 2013. Some information may be outdated.

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

/s/

DINKO REKIC
10/22/2015

JIANG LIU
10/22/2015

HUIFANG CHEN
10/22/2015

QIANYU DANG
10/22/2015

MICHAEL Y LI
10/22/2015

NORMAN L STOCKBRIDGE
10/22/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208434 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement #: S- N/A	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Alecensa (proposed) Established/Proper Name: alectinib Dosage Form: Capsule (oral) Strengths: 150 mg		
Applicant: Hoffmann-La Roche, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: July 6, 2015 – (last piece of rolling submission) Other submission dates; June 5 and June 19, 2015 Date of Receipt: July 6, 2015 Date clock started after UN: July 6, 2015		
PDUFA/BsUFA Goal Date: January 6, 2016		Action Goal Date (if different): N/A
Filing Date: September 6, 2015		Date of Filing Meeting: August 7, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For the treatment of ALK positive non-small cell lung cancer (NSCLC)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA – N/A	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 111723

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No N/A			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oped/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor requested exclusivity, but did not request a specific time frame.	
If yes , # years requested: Requested # of years not listed.					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>			X	
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ECTD submission - contains field copy certification
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan drug designation - exempt

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<i>forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

4

<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?⁵</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

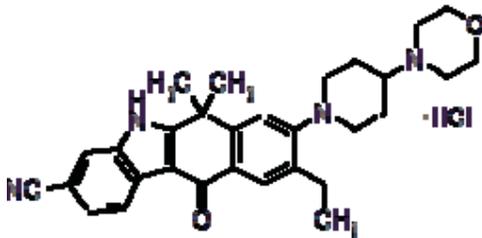
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT/IRT – requested July 14, 2015
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 14, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 7, 2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 7, 2015

BACKGROUND: Alectinib also RO5424802 or CH5424802 (proposed proprietary name Alecensa) is a small molecule inhibitor of ALK kinase. Hoffmann-La Roche (Roche) state that alectinib will be supplied commercially as an immediate release, 150-mg capsule, containing alectinib hydrochloride salt (equivalent to 150 mg of the free base); capsules are packaged in high-density polyethylene bottles with plastic closure with a desiccant, stored at (b) (4) °C.



A pre-NDA (Type B) clinical meeting was held April 7, 2015, between FDA and Roche under IND 111723. The purpose of this meeting was to discuss the results from Studies NP28761/AF-002JG and NP28673 and to reach agreement on the content and format of a proposed NDA to support a request for accelerated approval for the proposed indication under the PDUFA V Program.

A separate CMC pre-NDA meeting was held March 19, 2015 and meeting minutes were issued March 23, 2015.

For this NDA, the proposed indication is for the treatment of patients with ALK-positive, locally advanced or metastatic, non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gina Davis	Y
	CPMS/TL:	Melanie Pierce Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Gideon Blumenthal		Y
Division Director	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Erin Larkins	Y

	TL:	Gideon Blumenthal	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Stacy Shord	Y
	TL:	Hong Zhao	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Huanyu (Jade) Chen	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eias Zahalka Kim Ringgold	Y Y
	TL:	Emily Fox for Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Olen Stephens	Y
	RBPM:	Steven Kinsley	N
• Drug Substance	Reviewer:	Charles Jewell	Y
• Drug Product	Reviewer:	Rajiv Agarwal	Y
• Process	Reviewer:	Zhaoyang Meng	Y
• Microbiology	Reviewer:	Zhaoyang Meng	
• Facility	Reviewer:	Zhong Li	
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Olen Stephens		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Nathan Caulk	N

	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nazia Fatima	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Grace Jones	Y
	TL:	Alice (Chi-Ming) Tu	N
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Conner	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<p>referenced product(s)/published literature?</p> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment 	<input checked="" type="checkbox"/> YES

(EA) requested? If no , was a complete EA submitted? Comments: N/A	<input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments: N/A	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? N/A 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	N/A

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
September 25, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
N/A	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 60-day filing letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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

/s/

GINA M DAVIS
09/04/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208434

Application Type: New NDA

Name of Drug/Dosage Form: alectinib (proposed proprietary name Alecensa), 150 mg capsules

Applicant: Hoffmann-La Roche, Inc.

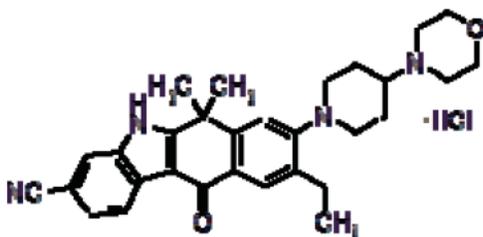
Receipt Date: July 6, 2015

Goal Date: January 6, 2016

Division Planned Action Goal Date: December 18, 2015

1. Regulatory History and Applicant's Main Proposals

Alectinib also RO5424802 or CH5424802 (proposed proprietary name Alecensa) is a small molecule inhibitor of anaplastic lymphoma kinase (ALK). Hoffmann-La Roche (Roche) state that alectinib will be supplied commercially as an immediate release, 150-mg capsule, containing alectinib hydrochloride salt (equivalent to 150 mg of the free base); capsules are packaged in high-density polyethylene bottles with plastic closure with a desiccant, stored at (b) (4) °C.



A pre-NDA (Type B) clinical meeting was held April 7, 2015, between FDA and Roche under IND 111723. The purpose of this meeting was to discuss the results from Studies NP28761/AF-002JG and NP28673 and to reach agreement on the content and format of a proposed NDA to support a request for accelerated approval for the proposed indication under the PDUFA V Program. A separate CMC pre-NDA meeting was held March 19, 2015 and meeting minutes were issued March 23, 2015. For this NDA, the proposed indication is for the treatment of patients with ALK-positive, locally advanced or metastatic, non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

- **No horizontal line separates Table of Contents from the FPI (# 3).**

Selected Requirements of Prescribing Information

- The following statement, “Because clinical trials are conducted under widely varying conditions, ^{(b) (4)} adverse reaction rates observed ^{(b) (4)} in ^{(b) (4)} clinical trials ^{(b) (4)} and may not reflect the rates observed in clinical practice” appears in Adverse Reactions, it does not precede the presentation of adverse reactions (#39).

1.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the filing letter or 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 18, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:**
- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:** *There is no horizontal line separating TOC from FPI.*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:**
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**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).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Selected Requirements of Prescribing Information

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form and one strength.*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: NME

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

GINA M DAVIS
09/04/2015

Division of Oncology Products 2 (DOP2) Labeling Review

NDA:	205266
SDN:	3
eCTD:	2
Submission date:	July 6, 2015
PDUFA goal date:	January 6, 2016
Review classification:	Priority
Proprietary (nonproprietary name):	Alecensa (alectinib)
Applicant:	Genentech USA, Inc.
Proposed Indication:	Alectinib is indicated for the treatment of patients with Anaplastic Lymphoma Kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Dosing regimen:	600 mg orally twice daily
Reviewer:	Jennie Chang, PharmD, Associate Director for Labeling

BACKGROUND:

Genentech USA, Inc. submitted an NDA for alectinib, a kinase inhibitor, on July 6, 2015. The Applicant is seeking approval in patients with Anaplastic Lymphoma Kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib at a proposed dose of 600 mg orally twice daily. The proposed indication is based on two pivotal Phase I/II, open-label, single arm, multicenter studies (NP28761/AF-002JG and NP28673) in patients with ALK-positive NSCLC who have progressed on previous crizotinib therapy.

Study NP28761 was a two-part, dose-finding (Part 1) and activity-estimating (Part 2), open-label, multicenter trial conducted in patients with locally advanced NSCLC not amenable to curative therapy (AJCC Stage IIIB) or metastatic NSCLC, with documented ALK rearrangement based on an FDA-approved test, and disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 following prior crizotinib. Patients were also permitted but not required to have progressed following prior chemotherapy. Patients in the first cohort (300 mg BID) of Part 1 were instructed to take alectinib under fasting conditions and all other patients were instructed to take alectinib with food.

The primary objective of the Part 2 was objective response rate (ORR) per RECIST v1.1 as assessed by independent radiological review committee (IRC). Secondary endpoints were safety,

progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR), central nervous system (CNS) objective response rate (CORR), CNS duration of response (CDOR), and CNS progression rate (CPR) at 3, 6, 9, and 12 months. An additional secondary objective of Study NP28761 is to assess quality of life (QoL) using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and QLQ-LC13). The primary analysis of Study NP28761 was to be conducted after all patients enrolled in Part 2 had completed 12 weeks of follow-up, unless they had progressed or died prior to week 12. The study was designed to reject the null hypothesis that ORR was \leq 35%.

Study NP28673 is a three-part, dose-finding (Part 1), activity-estimating (Part 2), and access (Part 3) trial conducted in patients with locally advanced NSCLC not amenable to curative therapy (AJCC Stage IIIB) or metastatic NSCLC, with documented ALK rearrangement based on an FDA-approved test, and disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 following prior crizotinib. Patients were also permitted but not required to have progressed following prior chemotherapy.

Alectinib was granted Breakthrough Therapy Designation for the treatment of patients with ALK-positive NSCLC with disease progression on crizotinib on June 26, 2013.

In this review, my proposed labeling recommendations and edits in the Alecensa labeling were annotated to the Applicant's labeling to ensure that the prescribing information would serve as a useful communication tool for healthcare providers and use clear, concise language. These recommendations and edits were based on regulations and guidances in order to convey the essential scientific information needed for the safe and effective use of Alecensa.

The following pages contain the working version of the Alecensa labeling with my recommended edits and comments (identified as 'JC3' through 'JC74'). Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DOP2's final recommendations for the Alecensa labeling.

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

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/s/

JENNIE T CHANG
09/03/2015

PMR/PMC Development Template

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

NDA/BLA #	NDA 208434
Product Name:	Alectinib (Alecensa)
<i>PMR 2015-1</i> PMR/PMC Description:	<div style="background-color: #cccccc; width: 100%; height: 40px; display: flex; align-items: center; justify-content: center;">(b) (4)</div>

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>March 2014</u>
	Study/Trial Completion:	<u>March 2019</u>
	Final Report Submission:	<u>June 2018</u>
	Other: <u>n/a</u>	

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

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

The proposed PMR is the submission of the clinical study report for an ongoing randomized study of alectinib versus crizotinib for treatment-naïve patients with locally advanced or metastatic non-small cell lung cancer whose tumors harbor ALK rearrangement. The subgroup of non-small cell lung cancer patients to be studied in this trial and the subgroup of non-small cell lung cancer patients studied in the earlier phase trials (patients with metastatic non-small cell lung cancer whose tumors harbor ALK rearrangement and whose disease progressed following crizotinib therapy), are populations of patients for whom alectinib potentially provides substantial improvement over available therapy for a life threatening condition. This was the basis for granting breakthrough therapy designation to alectinib, and the basis for the accelerated approval of alectinib.

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

The accelerated approval of alectinib was based on single-arm study information. Efficacy and safety data was not compared to a randomized control arm, and this has implications for interpretation of the data. Regular approval is contingent on demonstration of efficacy and safety against a control arm of appropriate available therapy in a related population that is capable of verifying the predicted clinical benefit.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

At least one randomized clinical trial establishing the superiority of alectinib over available therapy as determined by progression-free or overall survival in patients with metastatic ALK-positive non-small cell lung cancer.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

ERIN A LARKINS
12/11/2015

GIDEON M BLUMENTHAL
12/11/2015

JEFFERY L SUMMERS
12/15/2015

OSI CONSULT: Request for Clinical Inspections

Date: 7/10/2015

To: Lauren Iacono-Connor, Ph.D.
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Erin Larkins, DOP2*
Gideon Blumenthal, DOP2

From: *Gina Davis, DOP2*

Subject: Request for Clinical Site Inspections

I. General Information

Application#: 208434

IND#: 111723

Applicant: Hoffmann-La Roche Inc.

Regulatory Point of Contact: Chez Min Murdoch, Regulatory Program Management

Regulatory Point of Contact Phone: 650-273-3195

Regulatory Point of Contact E-mail: murdochc@gene.com

Drug Proprietary Name: Alecensa

Generic Drug Name: alectinib

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of ALK positive non-small cell lung cancer

PDUFA: TBD

Action Goal Date: TBD

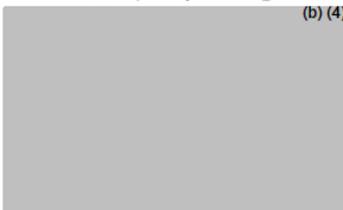
Inspection Summary Goal Date: TBD

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Gadgeel, Shirish Wayne State University Karmanos Cancer Center 4100 John R, 4 HWCRC Detroit, MI 48201 phone: 313-576-8753 fax: 313-576-8699 email: gadgeels@karmanos.org	261586	NP28761	14	Phase I/II Study of the ALK Inhibitor CH5424802/RO5424802 in Patients with ALK-Rearranged Non-Small Cell Lung Cancer Previously Treated with Crizotinib
Ou, Sai-Hong University of California Irvine 101 The City Drive South Bldg 56, Rte 8, Rm 241 Orange, CA 92868 phone: 714-456-8104 fax: 714-456-2242 email: ignatius.ou@uci.edu	261589	NP28761	27	Phase I/II study of the ALK inhibitor CH5424802/RO5424802 in patients with ALK-rearranged non-small cell lung cancer previously treated with crizotinib
Ou, Sai-Hong University of California Irvine 101 The City Drive South Bldg 56, Rte 8, Rm 241 Orange, CA 92868 phone: 714-456-8104 fax: 714-456-2242 email: ignatius.ou@uci.edu	259878	NP28673	5	An open-label, non-randomized, multicenter phase I/II trial of RO5424802 given orally to non-small cell lung cancer patients who have ALK mutation and who have failed crizotinib treatment

Tentatively requesting Contract Research Organization (CRO) inspection (with OSI to confirm):



III. Site Selection/Rationale

Site Information

STUDY:	NP28761	SITEID:	261586
---------------	---------	----------------	--------

NAME	Gadgeel, Shirish
LOCATION	Wayne State University, Karmanos Cancer Center 4100 John R, 4 HWCRC Detroit, MI 48201
PHONE/FAX	313-576-8753 / 313-576-8699
EMAIL	gadqeels@karmanos.org

Rationale: Second highest enrolling site.

Site Information

STUDY:	NP28761	SITEID:	261589
---------------	---------	----------------	--------

NAME	Ou, Sai-Hong
LOCATION	University of California Irvine 101 The City Drive South, Bldg 56, Rte 8, Rm 241 Orange, CA 92868
PHONE/FAX	714-456-8104 / 714-456-2242
EMAIL	ignatius.ou@uci.edu

Rationale: Highest enrolling site. Site participated in both of the main studies supporting this NDA.

Site Information

STUDY:	NP28673	SITEID:	259878
---------------	---------	----------------	--------

NAME	Ou, Sai-Hong
LOCATION	University of California Irvine 101 The City Drive South, Bldg 56, Rte 8, Rm 241 Orange, CA 92868
PHONE/FAX	714-456-8104 / 714-456-2242
EMAIL	ignatius.ou@uci.edu

Rationale: Highest enrolling site in U.S. Site participated in both of the main studies supporting this NDA.

Site Information

STUDY:	(b) (4)	SITEID:	N/A - CRO
---------------	---------	----------------	-----------

NAME	(b) (4)
LOCATION	
PHONE/FAX	
EMAIL	

Rationale: (b) (4) was responsible for independent radiology review for Studies (b) (4). The primary endpoint for both studies is objective response rate (ORR) based on independent review committee (IRC) assessment.

Rationale for OSI Audits

This is an NDA for a new molecular entity (NME). The sites selected for audit for Study NP28761 are the two highest enrolling sites. Results from these sites could potentially have significant impact on the efficacy results of Study NP28761. Dr. Sai-Hong Ou's site at the The University of California Irvine participated in both of the main studies, NP 28761 (Site ID 261589) and NP28673 (Site ID 259878), submitted to support efficacy for the current NDA. This site enrolled the highest number of subjects to Study NP28761 and was one of the two highest accruing sites (5 patients each) in the United States for Study NP28763.

The primary endpoint for both studies is ORR based on IRC assessment. (b) (4) was responsible for independent radiology review for Studies (b) (4)

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Site participated in both of the main studies supporting this NDA.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). High enrolling sites are all foreign, this is for an NME in a vulnerable population with limited medical options, needed to support application

IV. Tables of Specific Data to be Verified (if applicable)

N/A

Should you require any additional information, please contact *Gideon Blumenthal* at 301-796-5369 or *Erin Larkins* at 240-796-4286.

Concurrence: (as needed)

Gideon Blumenthal Medical Team Leader
Erin Larkins Medical Reviewer

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/s/

GINA M DAVIS
07/10/2015